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When comorbidity prevalence is over 50%, doubts about the validity of the diagnosis may be raised. If comorbidity is so common, does this reflect a weakness of the diagnosis? Does it mean that the comorbidity itself should be a diagnosis? Or do the comorbid conditions reflect one underlying entity, with common etiology, expressed in two different phenotypes? This might be the case with anxiety and depression. Actually, they are so clearly linked that the relationship resembles many a Möbius strip (see logo above). Like in the Möbius strip, when looking at it, it is impossible to say where one edge ends and another begins.

Cutting along the middle of a Möbius strip makes a similar construct, more twisted, but larger and more easily examined and described. Cutting along the middle of the new, larger shape results in two separate loops; each more twisted, and very closely intertwined, but nevertheless two distinct entities. It remains to be seen whether continued research will reveal comorbid anxiety and depression to be two intertwined disorders or a single pathology with two different phenotypes. The hope is that using various underlying endophenotypical tools will assist in unraveling the nature of the anxiety-depression coalition. Others refer to the relationship as the legendary Gordian Knot, a knot so complex that no one could untie it. Alexander the Great, so the legend says, did it his way—cutting it with his sword.

Could endophenotype replace Alexander the Great’s sword? Would looking beyond (or deeper than) the phenotype, the symptom, the clinical presentation, help? Would using synergistically integrated data derived from genetics, brain circuits, and clinical neuroscience be the key? Will a combination of getting closer and gaining a deeper understanding of the electrophysiology of the disorder take us further? Would laboratory-based evaluations of negativity, and fear conditioning and extinction provoked by specific neurocognitive tasks provide us with the answer?

Psychiatry has been struggling with diagnostic issues for many years. Before the Diagnostic and Statistical Manual of Mental Disorders (DSM)–III, both the reliability and validity of psychiatric diagnoses were low. Diagnostic reliability improved with DSM-III and DSM-IV, but validity remains unsatisfactory. The focus of the journey over the past 30 years has been on refinement of clinically based classification. However, diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics. At present, we are trying to provide a better match between research findings and clinical decision-making, the ex-
pectation being that this will lead to better validity. The hope is that using new technologies to quantify connectivity in vivo, including imaging, genomics, and early life programming, together with clinical neuroscience, will lead to discovery of the relevant biosignature and hence pave the way to recognition of the anxiety-depression “Siamese twins” phenotype.

Although these approaches may seem futuristic and out of reach, there are clear models that speak to their feasibility and practicality. Chamberlain et al.2 combined specific cognitive challenge (reversal learning) with functional brain imaging to look at development of a potential endophenotypic tool to improve classification of disorders proposed to be part of the obsessive-compulsive disorder (OCD) spectrum. Their approach used specific cognitive signatures to identify (in real time) relevant brain circuitry (via functional magnetic resonance imaging [fMRI]). This was examined in patients and in non-affected family members.

In 2010, the National Institute of Mental Health (NIMH) announced the Research Domain Criteria (RDoC) initiative, and suggested creating a framework for diagnosis based on research in pathophysiology, especially focused on genomics and neuroscience. RDoC is intended to ultimately provide a framework for classification based on empirical data from genomics and neuroscience, as the authors believe that progress in psychiatry is hampered by a fixation on the convenience of clinging to the familiar, phenotypically-based and consensually-agreed clinical diagnoses.

In other areas of medicine, these kinds of “revolutions,” overcoming the existing, agreed-upon, pharmacological-based, and symptom-driven diagnostic framework is unfolding. One example is in ophthalmology: the case of “dry” and “wet” age-related macular degeneration. “Dry” macular degeneration (DMD) looks very different through the ophthalmoscope as compared with "wet" macular degeneration (WMD). Indeed, until recently (2006), they were regarded, read about, and taught as two separate disorders. Only when examining the CFH Y402H allele did it become apparent that they are different manifestations of the same disorder.5

Would classification based on genomics and neuroscience, as well as clinical observation, bring us nearer to the goal of improving treatment outcomes? Would sophisticated use of advanced high-technology like quantifying connections in vivo, combined with imaging genomics, flatten out and clarify the twists of the Möbius strip?

Could advanced epigenetic models—including early life programming with integration of laboratory-based evaluation of negative emotional resonance, fear conditioning and extinction challenges—coupled with synchronization of structural and functional brain mapping replace Alexander the Great’s sword and untie the anxiety-depression Gordian Knot? The critical test will be how well the new molecular and neurobiological parameters predict prognosis and treatment response. One potential avenue is to replace the binary (dichotomous) approach to diagnosis with a dimensional matrix. The columns would host genetics, circuitry, early life programming, electrophysiology, fear extinction, negative emotionality, etc. and the lines would include the existing (and yet to be developed) clinically relevant dependent variables such as measures of depression, scores of fear; quantified level of distress, dimensions of impulsivity, coping styles, etc.

In this system, the focus would be on fear extinction (instead of anxiety), emotional bias (negative emotionality in depression), cognitive deficits (schizophrenia), cognitive flexibility (e.g., reversal learning in OCD), impulsivity, and temperament would all be considered potential domains.

All of these points are reflections for the future. Meanwhile, you are invited to an updated, cutting-edge, fine snapshot of the current state of the art. A superb overview is provided to you by the finest researchers and writers in the field. So, enjoy this unique collection of exceptional papers. They certainly provide the springboard for diving into the deep waters of the anxiety-depression phenomenon. ■

Keywords: anxiety; comorbidity; depression; diagnosis; macular degeneration; phenotype

References

Selected abbreviations and acronyms
- DMD: dry macular degeneration
- DSM: Diagnostic and Statistical Manual of Mental Disorders
- fMRI: functional magnetic resonance imaging
- NIMH: National Institute of Mental Health
- OCD: obsessive-compulsive disorder
- RDoC: Research Domain Criteria
- WMD: wet macular degeneration
Lorsque la prévalence d’une comorbidité dépasse 50 %, des doutes sur la validité du diagnostic peuvent être soulevés. Si la morbidité est aussi fréquente, cela reflète-t-il une faiblesse du diagnostic ? Cela signifie-t-il que la comorbidité elle-même constitue un diagnostic ? Ou les affections comorbides reflètent-elles une entité sous-jacente, d’étiologie commune, exprimée par deux phénotypes différents ? Cela pourrait être le cas avec l’anxiété et la dépression. En effet, elles sont si nettement associées que leur relation ressemble pour beaucoup à un ruban de Möbius. Et comme le ruban de Möbius, lorsqu’on l’examine, il est possible de dire où finit un bord et/ou commence l’autre.

En coupant longitudinalement au milieu un ruban de Möbius, on obtient une structure similaire, plus torsadée, mais de longueur plus importante et plus facile à examiner et à décrire. Couper au milieu de la nouvelle forme plus large produit deux boucles séparées ; encore plus torsadées, et très étroitement entrelacées, mais deux entités distinctes. Il reste à savoir si les recherches futures révéleront si l’anxiété et la dépression comorbides sont deux troubles étroitement liés ou une pathologie unique s’exprimant par deux phénotypes différents. L’espoir réside dans le fait que l’analyse du phénotype avec différents outils d’endophénotypiques... contribuera à révéler la nature de la coalition anxiété-dépression. D’autres font référence à la relation de l’anxiété et de la dépression en évoquant le légendered nœud gordien, un nœud si complexe que personne ne pouvait le défaitre. Alexandre le Grand, selon la légende, résolut le problème à sa manière – en le tranchant avec son épée.”

L’endophénotype pourrait-il remplacer l’épée d’Alexandre le Grand ? Examiner au-delà (ou plus en profondeur) du phénotype, du symptôme, du tableau clinique, peut-il être utile ? La solution consiste-t-elle à utiliser des données intégrées de manière synergique provenant de la génétique, des circuits cérébraux et des neurosciences cliniques ? Aller plus près et à la fois comprendre plus en profondeur l’électrophysiologie du trouble, les évaluations biologiques de la négativité et le conditionnement et l’extinction de la peur par des tâches neurocognitives spécifiques nous apportera-t-il la réponse ?

La psychiatrie se débat avec des problèmes diagnostiques depuis de nombreuses années. Avant la parution du Manuel Diagnostique et Statistique des Troubles Mentaux III (DSM-III), la fiabilité et la validité des diagnostics psychiatriques étaient faibles. La fiabilité des diagnostics s’est améliorée avec le DSM-III et le DSM-IV, mais la validité est restée insuffisante. Tous les efforts des 30 dernières années se sont
portés sur une amélioration de la classification clinique. Cependant, les catégories diagnostiques basées sur un consensus clinique n’ont pas montré de correspondance avec les découvertes faites dans les domaines des neurosciences cliniques et de la génétique. À l’heure actuelle, nous essayons d’atteindre un meilleur appariement entre les résultats des recherches et les prises de décision cliniques, en espérant que cela conduise à une meilleure validité.

Les espoirs se portent sur le fait que l’utilisation des nouvelles technologies pour quantifier la connectivité in vivo, notamment l’imagerie, la génomique, et la programmation en début de vie, en association avec les neurosciences cliniques, pourra conduire à la découverte d’une biosignature significative, et par conséquent tracera la voie vers la reconnaissance du phénomène de ces sœurs siamoises que sont l’anxiété et la dépression.

Bien que ces approches puissent sembler futuristes et hors de portée, il existe des modèles clairs plaçant pour leur faisabilité et leur capacité d’être mises en pratique. Chamberlain et coll. ont associé des épreuves cognitives spécifiques (apprentissage inverse) avec un système cérébral fonctionnel afin d’examiner le développement d’un outil endophénytopik potentiel permettant d’améliorer la classification des troubles supposés appartenir au spectre des troubles obsessionnels compulsifs (TOC). Leur approche a reposé sur l’utilisation de signatures cognitives spécifiques permettant d’identifier (en temps réel) les circuits cérébraux correspondants (en utilisant l’imagerie par résonance magnétique fonctionnelle [IRMf]). Cette méthode a été utilisée chez des patients et chez des parents non affectés.

En 2010, l’Institut National de la Santé Mentale (National Institute of Mental Health, NIMH) a annoncé l’initiative RDoC (Research Domain Criteria, critères de domaines de recherche), et a suggéré la création d’un cadre visant à baser le diagnostic sur des recherches en physiopathologie, en particulier en génomique et en neurosciences. Les RDoC sont destinés en définitive à un cadre de classification basé sur des données empiriques issues de la génétique et des neurosciences, dans la mesure où les auteurs considèrent que les progrès en psychiatrie ont été entravés par la facilité consistant à se raccrocher aux diagnostics cliniques, phénoménytopiques et consensuels.

D’autres domaines de la médecine connaissent ce type de « révolution » qui permet de dépasser le diagnostic existant, convenu et basé sur les symptômes et la pharmacologie. Un exemple peut être cité en ophtalmologie : le cas de la dégénérescence maculaire liée à l’âge, qui peut être soit « sèche » soit « humide ». La dégénérescence maculaire « sèche » (DMS) a un aspect très différent à l’ophtalmoscope par rapport à la dégénérescence maculaire « humide » (DMH). En effet, jusqu’à une période récente (2006), ces deux formes étaient considérées, présentées et enseignées comme deux troubles séparés. Ce n’est qu’en examinant l’allèle CFH Y402H qu’il est apparu qu’il s’agissait de deux manifestations différentes du même trouble.

Une classification basée sur la génomique et les neurosciences, ainsi que sur l’observation clinique, nous rapprochera-t-elle de l’objectif visant à améliorer les résultats thérapeutiques ? L’utilisation habile des hautes technologies avancées, par exemple la quantification des connexions in vivo, combinée à l’imagerie génomique, permettrait-elle d’aplanir et de clarifier les torsions du ruban de Möbius ?


L’une des voies potentielles serait de remplacer l’approche diagnostique binaire (dichotomique) par une matrice dimensionnelle. Les colonnes correspondaient à la génétique de l’hôte, les circuits, la programmation de début de vie, l’électrophysiologie, l’extinction de la peur, l’émotivité négative, etc., tandis que les rangées correspondaient aux paramètres dépendants cliniquement significatifs existants (et à développer), notamment les mesures de la dépression, les scores de peur, le niveau quantifié de détresse, les dimensions de l’impulsivité, les styles d’adaptation, etc.

Dans ce système, l’accent doit être mis sur l’extinction de la peur (au lieu de l’anxiété), les biais émotionnels (émotivité négative dans la dépression), les déficits cognitifs (schizophrénie), la flexibilité cognitive (par exemple, apprentissage inverse dans les TOC), l’impulsivité et le tempérament devraient tous être considérés comme des domaines potentiels.

Tous ces points sont des réflexions pour l’avenir. En attendant, vous êtes invités à découvrir de façon détaillée les dernières avancées de l’état des connaissances. Un superbe aperçu vous sera présenté par les chercheurs et les rédacteurs les plus renommés dans ce domaine. Profitez de ce recueil unique d’articles exceptionnels. Ils constitueront certainement le tremplin qui vous permettra de plonger dans les eaux profondes du phénomène de l’anxiété et de la dépression.
What do a Bach canon, a bald soprano, and a parade of ants have in common? Why, a simple strip, albeit one with fascinating properties. Bach unwittingly anticipated Möbius, in musical terms at least, by some 150 years, Ionesco’s play La Cantatrice Chauve is looplike in structure, and M. C. Escher’s woodcut, well those ants never tire of marching around the single unending surface of their Möbius strip. Discovered in 1858 by August Ferdinand Möbius, a German mathematician and astronomer and descendant of none other than Martin Luther, and independently in the same year by another German mathematician, Johann Benedict Listing, the Möbius strip has found its way into the inner recesses of the human imagination.

Give a strip of paper a half-twist (180°) and glue the ends together to form a loop. You now have a Möbius strip. It’s that simple. And strange. The Möbius strip has only one surface and one edge, which is topologically equivalent to a circle. Scissor the strip down the middle and you’ll end up not with two separate loops, as one might imagine, but a single long one with two full twists. Place an ant on a Möbius strip, give it a nudge, and watch as it crawls along the entire length of the strip, on both sides of the paper, before ending up back where it started. And in 3-D Euclidean space the Möbius strip can be clockwise or counterclockwise, depending on the direction of the half-twist. It is chiral, meaning it has (right- or left-) handedness, is not identical to, and cannot be superposed on, its mirror image. Human hands are a good example of chirality: try using your left hand to shake someone else’s right.

But Möbius’s discovery didn’t just herald mathematical fun and games, cerebral whimsy. His strip has applications. In mathematics, of course, but also in engineering (conveyor belts that last longer because instead of just one side of the belt both are used, so wear and tear is halved), organic chemistry (Möbius aromaticity), electronic circuitry (the Möbius resistor resists the flow of electricity yet does not simultaneously generate magnetic interference), nanoarchitecture (DNA origami may prove useful in creating drug-delivery nanosystems), peptide chemistry (insecticidal Möbius cyclotides expressed in plants show therapeutic potential as anti–human immunodeficiency virus agents). Möbius the mathematician is not to be confused with his namesake, one Paul Julius Möbius (1853-1907), a German neurologist after whom the Möbius syndrome—a congenital form of facial paralysis—is named. But our strip man, August Ferdinand, is very much at the center of this issue of Medicographia, which poses the question: are anxiety and depression distinct entities or do they in fact form a continuum, akin to a Möbius strip?
Categorical and dimensional approaches to conceptualizing and assessing psychiatric syndromes and symptoms are complementary rather than mutually exclusive. A categorical approach provides a clinically useful way to communicate rapidly the main features of a case. A dimensional perspective allows for a more fine-grained approach. It is useful to employ categorical and dimensional approaches in tandem, in both clinical and research settings.

Dimensional or categorical: different classifications and measures of anxiety and depression

by D. J. Stein, South Africa

Psychiatric syndromes and symptoms are complex phenomena that can potentially be conceptualized and assessed both categorically and dimensionally. Both the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Disease (ICD) systems rely extensively on a categorical approach, but also note the dimensional nature of syndromes and symptoms. Here, some of the relevant conceptual issues for anxiety and mood disorders are reviewed, and exemplars from the DSM and ICD revision process are used to illustrate these issues. Categorical diagnoses and specifiers are often useful, although they also have key limitations that should be recognized. Dimensional ratings allow for more fine-grained conceptualization and assessment of symptom profiles and etiological factors; this may have some benefits, but also some costs. Categorical and dimensional approaches should be seen as complementary, and may usefully be employed in tandem.

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**Categorical approaches**

A categorical approach to psychiatric disorders is frequently adopted in clinical practice, because the presence or absence of a particular condition crucially informs treatment decisions. Although symptoms are often measured dimensionally, categorical cut points are then used to make a determination about treatment. The utility of categories is not limited to the clinic; psychiatric epidemiologists may, for example, find it useful to record details about a history of lifetime major depression, and intervention researchers may find it useful to determine categorical treatment response, even if statistical methods demonstrate that depressive symptoms fall on a continuum (i.e., there is no underlying taxon).4

A categorical approach to conceptualizing and assessing psychiatric disorders has several major limitations that deserve recognition. A first problem is encouraging what may be termed “essentialism.” Major depression is not a “natural kind” in the same way that say gold or silver is.15 First, two individuals with major depression may have quite different symptom profiles and symptom severity. Second, two individuals with major depression may have quite different factors contributing to the pathogenesis of symptoms; these may differ both in type and extent (e.g., one patient may have several minor genetic variants contributing to an episode; a second patient may have one major genetic variant that is responsible).

Nevertheless, the provision of categories such as “major depression,” defined in terms of operationalized criteria, means that such entities may be reified, and viewed as natural kinds. This may have significant negative consequences in clinical and research contexts. First, clinicians may focus their clinical assessment primarily on the operational criteria provided in the nosological systems rather than on many other kinds of symptoms and contexts which may also be clinically relevant. Second, clinicians may not only fail to appreciate the complexity of symptomatology, but they may also overlook the complexity of contributing factors, focusing, for example, on particular genetic and environmental risk factors at the expense of others.

The use of a categorical approach may lead, then, to a systematic underappreciation of the importance of variations in overt symptoms and in underlying mechanisms from individual to individual. One patient may have typical symptoms of a mild degree in one kind of situation, while another patient may have atypical symptoms of a moderate degree caused by a quite different range of factors. The type and extent of depressive and anxiety symptoms may differ across gender, developmental stage, and culture; such differences may be downplayed or ignored by using a single category, such as “generalized anxiety disorder,” to describe anxiety symptoms in each of these cases. Such dimensional variation may occur even in disorders where discontinuity in symptom measures indicates an underlying latent taxon (e.g., schizotypy).4

Another important problem with the categorical approach is that when the DSM system is employed, many individuals are found to have more than one disorder. Such extensive comorbidity seems artifactual. Individuals with both major depression and generalized anxiety may arguably, for example, be more accurately conceptualized as having a mixed anxiety depressive disorder.10 Diagnosing individuals with two comorbid disorders would seem to suggest that each involves different etiological mechanisms and requires different treatments, when a more parsimonious approach may be more accurate. (The entity of subthreshold mixed anxiety disorder remains, however, controversial.)11 A final problem with a categorical approach is particularly important in research settings; analyses of dimensional measures offer greater statistical power.

**Dimensional approaches**

Given these kinds of difficulties raised by the categorical approach, many clinicians and researchers advocate the use of a dimensional approach to conceptualizing and assessing psychiatric syndromes and symptoms. Given that nature cannot easily be carved at her joints, one argument is that an understanding of the psychobiology of psychiatric disorder requires an acceptance of the dimensional nature of symptoms.10 Dimensions can conceivably be used to record not only symptom profiles, but also etiological contributors, including the full range of relevant types and extents. Indeed, there have been ongoing efforts to include a dimensional approach in DSM-5.13-15 Such dimensions may include continuous assessment of core symptoms, dimensional assessments that cut across different disorders, and spectrum constructs.16

At the same time, it should be noted that there are also potential problems with a dimensional approach. First, dimensional analysis is only useful when the association of predictors with dimensional scores is in fact constant throughout the relevant dimensional severity range.4 Second, the use of dimensions does not necessarily avoid essentialism and reification; instead of there being reification of a single entity, there is potentially reification of particular symptoms or causal dimensions. Third, while artifactual comorbidity may be diminished, there is potentially the problem of how to easily articulate complex patterns of overt symptoms and underlying mechanisms. Thus, for example, the use of just 3 dimensions requires 8 categories based on high and low cut-off scores to articulate constructs situated at the high and low ends of these dimensions. This creates difficulties for both clinicians and researchers, and raises issues of user acceptability.17

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Disease</td>
</tr>
<tr>
<td>OCD</td>
<td>obsessive-compulsive disorder</td>
</tr>
<tr>
<td>SAD</td>
<td>social anxiety disorder</td>
</tr>
</tbody>
</table>
### Presence of a diagnosis of OCD

- Yes

### Presence of obsessions as defined in DSM-IV-TR

- Yes, in most cases

### Presence of compulsions as defined in DSM-IV-TR

- Yes, in most cases

### Presence of clinically significant hoarding

- Possible, but rare (approximately 5% of cases)
- Clinician needs to ascertain if hoarding is secondary to other OCD themes (e.g., fears of contamination or harm) or an independent (i.e., comorbid) problem. The latter is more common

### Presence of a diagnosis of OCPD

- Possible, in approximately one-fourth of cases

### Insight

- It varies, but good in most cases

### Help-seeking behavior

- Many sufferers seek help, although this may take several years

### Stability of problem

- Symptoms can wax and wane
- Approximately 2%

### Prevalence

- Yes
- Yes (27%-47% genetic in adults, higher in children)

### Familial

- Fronto-striatal-thalamic circuits

### Heritable

- Cingulate cortex and ventral frontal and limbic regions

### Neural substrates

- Large body of evidence
- Overestimation of threat/responsibility
- Importance/control of thoughts
- Perfectionism/need for certainty

### Cognitive processes

- Compulsive behavior in OCD is negatively reinforced via avoidance conditioning (avoiding distress, feared consequences, etc), but there is no positive reinforcement of OCD symptoms

### Reinforcement patterns

- Moderate to good
- Large body of evidence

### Treatment response (CBT and SRIs)

- Poor to moderate
- Limited evidence

### OCD

- Possible as a comorbid condition (approximately 20% of cases), but OCD not most frequent comorbidity
- Mood and anxiety disorders more frequent
- Fears of losing important things resemble and may be functionally similar to obsessions
- Absence of intrusive, unwanted and repugnant thoughts, images, or impulses that are actively resisted

### Compulsive hoarding

- Intense distress often triggered when sufferers face the prospect of having to discard possessions
- Avoidance of discarding and acquisition behaviors may be functionally similar to compulsions
- Always. Hoarding due to practical or sentimental reasons
- If comorbid with OCD, hoarding not secondary to other OCD symptoms or magically linked to classic obsessional fears

### Table I. Differences between compulsive hoarding and obsessive-compulsive disorder.

**Abbreviations:**
- CBT, cognitive behavioral therapy
- DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-IV-text revision
- OCD, obsessive-compulsive disorder
- OCPD, obsessive-compulsive personality disorder
- PD, personality disorder
- SRI, serotonin reuptake inhibitor

Indeed, dimensional approaches are often translated back into categorical approaches via the use of cut points. Thus, in clinical settings, patients with scores above a particular cut point on a symptom severity rating scale may be viewed as having the relevant disorder, while those with scores below this cut point may be viewed as not having the condition. Fortunately, the research literature has provided a growing body of information on the relationship between coarse-grained, but user-friendly categorical measures, and more fine-grained, dimensional measures. Thus, for example, in the World Mental Health Surveys, tandem use of categorical and dimensional measures allowed validation of cut points for assessing constructs such as psychological distress. Similarly, in treatment studies, the tandem use of categorical and dimensional measures allows a rigorous evaluation of optimal cut points for determining treatment response.

**Exemplars**

Is SAD a psychiatric disorder? Certainly, if one considers a patient with severe SAD symptoms and consequent symptoms of major depression, with associated marked distress and impairment, it seems clear that such an individual deserves to be diagnosed with a psychiatric disorder and to receive appropriate intervention. What about a patient who suffers from a single kind of performance anxiety, such as speaking in public, but who manages to avoid such situations, and who otherwise lives his or her life without distress or impairment? How about patients who are somewhat introverted and shy, but who find themselves in work situations that demand a high level of social interaction, where those who are more outgoing are rewarded with higher pay packages?

From a categorical perspective, DSM-IV differentiates between those with and without SAD on the basis of the so-called clinical significance criterion. This criterion indicates that individuals with marked clinical distress, or significant impairment as a consequence of their symptoms, meet the criteria for suffering from a clinical disorder. DSM-IV also differentiates individuals who have generalized SAD; such individuals fear “most” social situations. The literature suggests that individuals with generalized SAD have more severe symptoms, greater impairment, and are more likely to have a family history of SAD. Both “SAD” and “generalized SAD” seem to be clinically useful categories.

From a dimensional perspective, however, some individuals with social anxiety symptoms fear only a few different social situations, and others fear many. Individuals with many social fears who do not quite meet the clinical significance criterion may arguably still have significant symptoms, and may be at significant risk for comorbidity. The question of when to treat is one that should be decided using considerations such as cost-effectiveness. Similarly, there is no specific cut point that differentiates those with generalized versus non-generalized social anxiety; instead there is a monotonic dose-response relationship between number of social anxiety symptoms and indicators such as increased SAD persistence, severity, and comorbidity. Nevertheless, the distinction between generalized and nongeneralized may be important in other ways, such as in predicting treatment response.

Obsessive-compulsive disorder (OCD) provides another interesting exemplar. On the one hand, OCD seems a relatively homogenous neuropsychiatric entity, at least in comparison with disorders such as major depression or generalized anxiety disorder. On the other hand, there is growing evidence of the heterogeneity of OCD. For example, there is good evidence, based on meta-analysis of factor analytic studies of OCD symptom types, that OCD symptoms fall into a relatively limited number of key symptom dimensions. Also, there is evidence that OCD patients with and without comorbid tics may differ in important ways.

From a categorical perspective, the construct of OCD has long been supported on the basis of considerations of both diagnostic validity and clinical utility. On the other hand, the tic specifier that has been newly proposed for DSM-5 provides an additional category which allows an even more fine-grained assessment of patients with OCD. Again, this specifier seems to have both diagnostic validity as well as clinical utility. Thus, patients with OCD as well as tics are more likely to have particular kinds of symptom profiles, they may have different underlying genetic profiles, and they may respond differentially to intervention.

From a dimensional perspective, recording different OCD symptom dimensions may allow a more fine-grained level of assessment that is useful in both clinical and research settings. Thus, subjects with hoarding symptoms may have a different neurobiology and treatment response. Similarly, each of the major symptom dimensions in OCD may have some level of specificity at a neurological level. The DSM-5 proposal, however, is to recognize hoarding disorder as a separate clinical entity (Table I), and to describe OCD symptom dimensions in the text of the OCD section rather than as formal specifiers. This reflects data that hoarding symptoms represent a unique diagnostic category, while ratings of other symptom dimensions in OCD are perhaps less clinically useful.

Finally, there is the question of whether it is useful to assess obsessive-compulsive symptoms across a range of different anxiety disorders, and whether it is useful to have a separate chapter in the nosology on obsessive-compulsive spectrum disorders. Certainly, it has been suggested that the presence of obsessive-compulsive symptoms in disorders such as schizophrenia may have clinical utility. Furthermore, it has been argued that given overlaps in the phenomenology and psychobiology of several putative obsessive-compulsive spectrum disorders, it would enhance the scientific validity and clinical utility of the nosology to group such disorders together.
The inclusion of a separate chapter on obsessive-compulsive disorder and related disorders may help raise awareness of overlapping approaches to their diagnosis, assessment, and treatment. Several of these disorders may have similar dimensional specifiers, such as an insight specifier which ranges from good to poor (Table II).

At the same time, it should be acknowledged that any particular metastructure has both strengths and weaknesses. Thus, for example, a separate chapter on obsessive-compulsive and related disorders may lead to underemphasizing the important overlaps between OCD and other anxiety disorders (Table II). In addition, a separate chapter on obsessive-compulsive and related disorders runs the risk of downplaying important differences in the diagnosis, assessment, and treatment of different conditions that fall within this chapter. Placing obsessive-compulsive and related disorders immediately after the anxiety disorders in the DSM-5 metastructure may help emphasize relationships between these conditions, and it may be useful to emphasize in the DSM-5 text that there are important distinctions between each of the obsessive-compulsive and related disorders.

### Table II. Similarities between obsessive-compulsive disorder and selected obsessive-compulsive spectrum disorders.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Body dysmorphic disorder</th>
<th>Tourette’s disorder</th>
<th>Hypochondriasis</th>
<th>Trichotillomania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Comorbidity with OCD</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Familial relationship</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Treatment response</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Table III. Classification of delusional and nondelusional forms of disorders in DSM-IV.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Delusional and nondelusional forms classified together</th>
<th>Separate delusional disorder variant</th>
<th>Psychotic disorder NOS</th>
<th>Double coded</th>
<th>Poor insight specifier</th>
<th>Specification re: intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body dysmorphic disorder</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic mood disorder</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table IV. Cognitive deficits across anxiety disorders.

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>GAD</th>
<th>PD</th>
<th>SAD</th>
<th>Simple phobia</th>
<th>PTSD</th>
<th>OCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory</td>
<td>+++</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Attentional bias (emotional stroop and dot probe)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Increased baseline startle</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>?</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Cognitive flexibility (eg, WCST, ID/ED)</td>
<td>–</td>
<td>–</td>
<td>+a</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Response inhibition (eg, go/no go, SSRT)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Disgust sensitivity</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

+ = limited effect; ++ = moderate effect; +++ = strong effect; – = evidence of no effect; ? = no evidence. a When tested under stress.

### Conclusion

Categorical and dimensional approaches to conceptualizing and assessing psychiatric syndromes and symptoms are complementary rather than mutually exclusive, with dimensional assessments often informing categorical treatment decisions. Furthermore, categorical ratings can be transformed into dimensional ones (eg, by summing the number of diagnostic criteria met) and vice versa (eg, by using cut points to determine whether a categorical diagnosis should be made).

A categorical approach provides a clinically useful way to communicate rapidly the main features of a case, and is also valuable in particular research situations. A potential disadvantage of categorical approaches is that they may encourage reification and oversimplification of complex entities with multiple overt symptoms and underlying mechanisms. A dimensional perspective allows for a more fine-grained approach, but also has significant potential disadvantages. It is useful to employ categorical and dimensional approaches in tandem, in both clinical and research settings.

### Acknowledgment

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References

Keywords: anxiety disorder; categorical; dimensional; DSM-5; generalized anxiety disorder; ICD-11; major depression; mood disorder; obsessive-compulsive disorder; social anxiety disorder

Les symptômes et syndromes psychiatriques sont des phénomènes complexes qui peuvent être conceptualisés et évalués de façon catégorielle et dimensionnelle. Le DSM (Diagnostic and Statistical Manual of Mental Disorders) et l’ICD (International Classification of Disease) reposent largement sur une approche catégorielle mais constatent aussi la nature dimensionnelle des symptômes et des syndromes. Nous analysons ici certains concepts intéressants pour les troubles de l’humeur et de l’anxiété en les illustrant avec des exemples issus de la révision du DSM et de l’ICD. Diagnostiquer et spécifier de façon catégorielle est souvent utile même si il existe quelques limites à connaître. Les échelles dimensionnelles permettent une évaluation et une conceptualisation plus fines des profils symptomatiques et des facteurs étiologiques ; cela présente des avantages mais aussi des coûts. Les approches dimensionnelles et catégorielles doivent être vues comme complémentaires et employées utilement en tandem.

Dimensions ou catégorielles : les différentes classifications et mesures de l’Anxiété et de la Dépression
Mood and anxiety disorders are characterized by a variety of alterations in brain morphology and activity and in neuroendocrine disruptions. Comorbidity among anxiety and depressive disorders is particularly common and has significant implications in terms of clinical presentation, assessment, treatment selection and effectiveness, as well as the course of illness, prognosis, and long-term outcome. Despite this high comorbidity, many distinguishing features support the continued classification of individual anxiety disorders that are distinct from each other and from mood disorders. The traditional neurobiological concept of the etiology of depressive and anxiety disorders has been the monoamine hypothesis; however, in recent years, researchers have turned their attention to glutamate. Moreover, it has become evident that factors other than imbalances between neurotransmitter systems must be taken into account when describing the neurobiological basis of major depression in particular, but also of anxiety disorders; it is now well accepted that these conditions are characterized by internal desynchronization of information processing inducing profound alterations in brain structure, function, and responsiveness. The subsequent alterations in neuroplasticity and in inflammatory mechanisms are thought to be involved in the pathogenesis of the disorders.

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Via Stamira d’Ancona 20, Milano, Italy
(e-mail: smeraldi.enrico@hsr.it)

www.medicographia.com
 Anxiety and depression: The Möbius strip

Neurobiology and neurogenetics of anxiety and depression – Smeraldi

Neurobiological hypothesis

The traditional neurobiological concept of the etiology of depressive and anxiety disorders has been the monoamine hypothesis, which proposes that MDs are caused by a deficiency in serotonin or noradrenaline at functionally important receptor sites in the brain. Recent studies have provided strong evidence that glutamate and other amino acid neurotransmitters are involved in the pathophysiology and treatment of MDs. Studies employing in vivo magnetic resonance spectroscopy (MRS) have revealed altered cortical glutamate levels in depressed subjects and dysfunction of the predominant glutamatergic system. Malfunction in the mechanisms regulating clearance and metabolism of glutamate, and cytoarchitectural/morphological maladaptive changes in a number of brain areas mediating cognitive emotional processes have also been found. Consistent with a model of excessive glutamate-induced excitation in MDs, several antiglutamatergic agents have demonstrated potential antidepressant efficacy and glutamatergic modulators are available as antidepressants. Concurrently, studies on animal models have shown that different types of environmental stress enhance glutamate release/transmission in limbic/cortical areas and exert powerful structural effects, inducing dendritic remodeling, reduction of synapses, and possibly volumetric reductions resembling those observed in depressed patients. Considering anxiety disorders, drugs that reduce glutamate availability are hypothesized to possess anxiolytic properties. Elevated excitatory glutamatergic signaling associated with panicogenicity has been reported in patients affected by SAD who were shown to have a 13.2% higher glutamate/creatine ratio in the anterior cingulate cortex (ACC) as measured by MRS compared with healthy subjects. Moreover, as glutamate plays a critical role in hippocampal-dependent associative learning and in amygdala-dependent emotional processing in stressful conditions or following stress exposure, inappropriate glutamate signaling is believed to contribute to the processing distortion experienced by many patients who have PTSD. In support of the glutamate hypothesis of PTSD, the N-methyl-D-aspartic acid receptor antagonist ketamine is well-known for its ability to induce dissociative and perceptual distortions, similar to the processing distortion in patients affected by the disorder. There is growing evidence that disrupted neurotransmission of glutamate within cortico-striatal-thalamic-cortical circuitry plays a role in the pathogenesis of OCD. Candidate gene studies have identified associations between variants in glutamate system genes and OCD, particularly for SLC1A1 (the glutamate transporter gene). Furthermore, clinical studies using MRS found altered glutamate concentrations in the caudate and ACC of patients. Animal models also provided further indirect support for the role of glutamate dysfunction in OCD: in particular, the DLGAP3 (discs, large [drosophila] homolog-associated protein 3) and Strk5 knockout mouse models in fact display remarkably similar phenotypes of compulsive grooming behavior associated with glutamate signaling dysfunction.

During recent years, it has become evident that factors other than imbalances between neurotransmitter systems must be taken into account when describing the neurobiological basis of major depression and it is now well accepted that this condition is characterized by profound alterations in brain structure, function, and responsiveness. Recent evidence indicates that problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and suggest that disturbed neuroplasticity, including impaired adult hippocampal neurogenesis, might be implicated in the biological basis of the disorder. Antidepressant therapies are involved in the pathophysiology and treatment of MDs. Studies employing in vivo magnetic resonance spectroscopy (MRS) have revealed altered cortical glutamate levels in depressed subjects and dysfunction of the predominant glutamatergic system. Malfunction in the mechanisms regulating clearance and metabolism of glutamate, and cytoarchitectural/morphological maladaptive changes in a number of brain areas mediating cognitive emotional processes have also been found. Consistent with a model of excessive glutamate-induced excitation in MDs, several antiglutamatergic agents have demonstrated potential antidepressant efficacy and glutamatergic modulators are available as antidepressants. Concurrently, studies on animal models have shown that different types of environmental stress enhance glutamate release/transmission in limbic/cortical areas and exert powerful structural effects, inducing dendritic remodeling, reduction of synapses, and possibly volumetric reductions resembling those observed in depressed patients. Considering anxiety disorders, drugs that reduce glutamate availability are hypothesized to possess anxiolytic properties. Elevated excitatory glutamatergic signaling associated with panicogenicity has been reported in patients affected by SAD who were shown to have a 13.2% higher glutamate/creatine ratio in the anterior cingulate cortex (ACC) as measured by MRS compared with healthy subjects. Moreover, as glutamate plays a critical role in hippocampal-dependent associative learning and in amygdala-dependent emotional processing in stressful conditions or following stress exposure, inappropriate glutamate signaling is believed to contribute to the processing distortion experienced by many patients who have PTSD. In support of the glutamate hypothesis of PTSD, the N-methyl-D-aspartic acid receptor antagonist ketamine is well-known for its ability to induce dissociative and perceptual distortions, similar to the processing distortion in patients affected by the disorder. There is growing evidence that disrupted neurotransmission of glutamate within cortico-striatal-thalamic-cortical circuitry plays a role in the pathogenesis of OCD. Candidate gene studies have identified associations between variants in glutamate system genes and OCD, particularly for SLC1A1 (the glutamate transporter gene). Furthermore, clinical studies using MRS found altered glutamate concentrations in the caudate and ACC of patients. Animal models also provided further indirect support for the role of glutamate dysfunction in OCD: in particular, the DLGAP3 (discs, large [drosophila] homolog-associated protein 3) and Strk5 knockout mouse models in fact display remarkably similar phenotypes of compulsive grooming behavior associated with glutamate signaling dysfunction.

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>5-HTTLPR</td>
<td>5-HT transporter-linked polymorphic region</td>
</tr>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>COMT</td>
<td>catechol-O-methyltransferase</td>
</tr>
<tr>
<td>CSF CRF</td>
<td>cerebrospinal fluid corticotropin-releasing factor</td>
</tr>
<tr>
<td>DLGAP3</td>
<td>discs, large (drosophila) homolog-associated protein 3</td>
</tr>
<tr>
<td>DRD2</td>
<td>dopamine receptor D2</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GAD</td>
<td>generalized anxiety disorder</td>
</tr>
<tr>
<td>GSK3</td>
<td>glycogen synthase kinase 3</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>MD</td>
<td>mood disorder</td>
</tr>
<tr>
<td>MDD</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>OCD</td>
<td>obsessive-compulsive disorder</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
</tr>
<tr>
<td>PTSD</td>
<td>posttraumatic stress disorder</td>
</tr>
<tr>
<td>SAD</td>
<td>social anxiety disorder</td>
</tr>
<tr>
<td>SEFTP</td>
<td>serotonin transporter gene-linked polymorphic region</td>
</tr>
<tr>
<td>SLC1A1</td>
<td>glutamate transporter gene</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
</tbody>
</table>
Antidepressant treatments have been shown to normalize serum levels of inflammatory proteins and cytokines, including IL-1, IL-6, TNF-α and INF-γ. Wolkowitz et al postulated that inflammatory processes in major depression may be the underlying cause for early mortality, high rates of aging-related renal-medullary system function in patients with PTSD who suggested that changes occur in HPA axis and sympathetic-adrenergic system function in patients with PTSD who. Moreover, viral expression of Wnt2 in the hippocampus produces an antidepressant response in the learned helplessness and sucrose preference tests. These pathways have not been studied in anxiety disorders.

Recent studies support the concept that inflammatory mechanisms play a crucial role in the pathogenesis of major depression. Major depression has similarities with a chronic form of “sickness behavior,” a normal response to inflammatory cytokines. Elevations in proinflammatory cytokines and other inflammation-related proteins are well-documented in major depression and contribute to the hypercortisolism and decreased sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis found in the disorder, with adrenocorticotropic hormone (ACTH) responses being most attenuated in depressed patients with the most severe hypercortisolism. Moreover, roughly 30% of individuals treated with recombiant interferons develop depression as a side effect of treatment. Although administration of cytokines such as interferon-α or interleukin (IL)-6 was found to cause consistent depression-like features in rodents, recent preclinical studies indicate that blocking proinflammatory cytokine-mediated signaling can produce antidepressant effects. Mice with targeted deletions of the gene encoding IL-6 or those encoding the tumor necrosis factor (TNF)-α receptors show antidepressant-like behavioral phenotypes, and a centrally administered antagonist of the IL-1β receptor reversed the behavioral and antineurogenic effects of chronic stress.

Antidepressant treatments have been shown to act by inducing plastic changes in neuronal connectivity, which gradually lead to improvement in neuronal information processing, biological re-synchronization of brain circuits, and recovery of mood. Several signaling pathways and targets have been implicated, including the neurotrophic factor Wnt and glycogen synthase kinase 3 (GSK3) pathways. Microarray studies demonstrate that antidepressants differentially regulate the expression of Wnts, Fz, and Dsh receptors, and downstream transcription partners in the rodent hippocampus. Moreover, viral expression of Wnt2 in the hippocampus produces an antidepressant response in the learned helplessness and sucrose preference tests. These pathways have not been studied in anxiety disorders.

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tions between them, as occurs in normal development. As the hippocampus-amygdala complex has strong connections with the orbitofrontal cortex, these complexes are included in the OCD circuit. Abnormalities in the regions of the hippocampus and amygdala have been emphasized in studies involving PET or fMRI, and these regions have been suggested to play an important role in the pathophysiology of OCD. Moreover, in patients affected by OCD, a loss of normal hemispheric asymmetry of the hippocampus-amygdala complex and differences in amygdala volumes were found.

Two recent magnetic resonance imaging (MRI) structural studies in patients affected by panic disorder showed a volume reduction in the ACC or a relative gray matter deficit in the right ACC, with a significant gray matter increase in the left insula, the left superior temporal gyrus, the midbrain, and the pons. Typically, neuroimaging and postmortem analyses of patients with depression reveal structural changes in limbic and forebrain regions, including the hippocampus, amygdala, and PFC. Probably the most reproduced finding in the imaging of MD is a small (10%-15%), but significant, reduction in hippocampal volume as documented in MRI studies, with a positive correlation between the duration of the depressive episode and the reduction in hippocampal volume. Variation in gray matter volume was associated with GSK3β polymorphisms; the most significant associations were found for rs6438552, a putative functional intronic single nucleotide polymorphism (SNP) that showed 3 significant gray matter clusters in the right and left superior temporal gyri and the right hippocampus. Similarly, there are consistent reports of reduced PFC volumes in patients with depression, specifically in the dorsolateral PFC, orbitofrontal cortex, and subgenual PFC. Moreover, postmortem studies report a reduced size of pyramidal neurons and a decreased number of GABAergic interneurons and glia (both astrocytes and oligodendrocytes) in the PFC. Many of these effects also occur in response to chronic stress exposure in rodents and nonhuman primates, including atrophy of dendrites and spines in the PFC and hippocampus, and decreased glia numbers and neurogenesis in the adult hippocampus.

Volumetric changes have also been found in the amygdala in patients affected by MDD; these changes, however, appear to be dynamic throughout the course of depressive illness, with an initial enlargement, followed by a volume reduction as the illness progresses.

All the previously described regions are part of the limbic-cortico-thalamic circuit and are involved in the modulation of emotional and cognitive behavior. In patients affected by major depression, researchers have found morphological and functional alterations in these areas. Compared with healthy controls, patients affected by MDD have altered activation in the orbital and medial frontal cortex during exposure to emotionally charged stimuli and during performance of reward processing tasks. Moreover, one of the most consistent findings in the MD literature has been that patients with MDD show exaggerated activation in the amygdala when exposed to emotional stimuli.

It is also possible that emotional dysregulation could result from a lack of inhibition by the PFC on limbic structures, as suggested by the observation of decreased glucose metabolism in the PFC with increased metabolism in subcortical structures and fMRI studies showing reduced activity and impaired signal communication in corticolumnar networks critical to processing emotional stimuli.

Genetics

Each anxiety disorder, as well as MDD, has both genetic and environmental contributions to vulnerability. When attempting to identify the genetic contribution toward susceptibility to psychopathology, the candidate genes are largely the same across diagnoses and tend to be genes whose products regulate the HPA axis and monaminergic signaling. Ongoing research supports the hypothesis that a genetic predisposition may be shared among mood and anxiety disorders, with individual clinical manifestation being a product of both genetic and environmental influences. Some genetic factors are diagnosis specific; others are nonspecific, but influence the risk for psychopathology in general.

The most extensively studied variant in genetic studies of anxiety and MDDs is an SNP in the promoter region of the serotonin transporter gene (5-HTTLPR). This transporter is the target of the most widely used pharmacotherapy for anxiety disorders and MDDs, the selective serotonin reuptake inhibitors (SSRIs). The “short” allele of the 5-HTTLPR, lacking 44 base pairs of dinucleotide repeat sequence, confers reduced transcriptional activity to the serotonin transporter gene and has been associated with anxiety-related traits including neuroticism, harm avoidance, and, in some studies, anxiety disorders including social phobia, OCD, and PTSD. Regarding the association of the 5-HTTLPR polymorphism with depression, a gene-environment interaction was found. Short allele carriers seem to be more likely to develop depression after stressful life events than individuals homozygous for the long allele, and the same subjects seem to have an earlier age at onset, but a lower rate of illness recurrence. Moreover, a recent meta-analysis showed a significant association in MD between the long variant of the serotonin transporter gene-linked polymorphic region (SERTPR) and a better response to SSRI and chronobiological treatments. SERTPR was examined in OCD with regard to response to treatment: conflicting results were found, including evidence for a trend toward an association of poor response to SSRI in long-SERTPR as well as evidence for no association. The same polymorphism was found to influence...
brain morphometry in obsessive patients, with short-variant homozygotes having a smaller right orbito-frontal cortex than the long-variant homozygotes. In female patients affected by panic disorder, both homozygotes and heterozygotes for the SERTPR long variant were shown to have a better response to paroxetine than did homozygotes for the short variant.

Another gene studied both in mood and anxiety disorders is that encoding for catechol-O-methyltransferase (COMT). The COMT enzyme inactivates catecholamines, and the COMT Val(108)/Met polymorphism (rs4680) influences the enzyme activity with a trimodal distribution (high activity in Val/Val, intermediate activity in Val/Met, and low activity in Met/Met genotypes). A significant association was found between the polymorphism and early onset MD, particularly for the COMT Val/Val genotype. In MD, the methionine allele in the COMT Met variant has been associated with a worse response to mirtazapine, to paroxetine, and both a worse and better response to citalopram. Controversial results have been shown regarding the association of COMT gene polymorphism and OCD, while the same polymorphism has been implicated in susceptibility to panic disorder by several studies in independent samples. Moreover, in patients affected by panic disorder, Met homozygotes were found to show a poorer response both to paroxetine and to cognitive behavioral therapy.

The latest gene investigated both in mood and anxiety disorders is that encoding for the dopamine receptor D2 (DRD2). No association has been found with affective disorders, but DRD2 gene polymorphism has been shown to influence response to treatment in PTSD.

Conclusions

Although the traditional neurobiological concept of the etiology of depressive and anxiety disorders has been the monoamine hypothesis, focusing on serotonin, noradrenaline, and dopamine, in recent years, researchers have turned their attention to glutamate, the most important amino acid neurotransmitter. The glutamatergic system is considered a primary mediator of psychiatric pathology and—potentially a final common pathway for the therapeutic action of antidepressant drugs—is also used in the treatment of anxiety disorders. Moreover, during recent years, it has become evident that factors other than imbalances between neurotransmitter systems must be taken into account when describing the neurobiological basis of major depression in particular, but also of anxiety disorders; it is now well accepted that these conditions are characterized by desynchronization of brain circuits, causing profound alterations in brain structure, function, and responsiveness. There has been a paradigm shift from a monoamine hypothesis of depression to a neuroplasticity hypothesis, which focuses on glutamate. Recent evidence, in fact, indicates that problems in information processing within neural networks might underlie depression, and suggest that disturbed neuroplasticity, including impaired adult hippocampal neurogenesis, might be implicated in the biological basis of the disorder. Alteration in neuroplasticity has not been studied in anxiety disorders. Moreover, recent studies support the importance of inflammatory mechanism alteration in the pathomechanisms of both major depression and anxiety disorders.

Acknowledgment

The author would like to thank Dr Sara Dallasepezia for her collaboration.

References


47. Benedetti F, Barbini B, Bernasconi A, et al. Lithium overcomes the influence of 5-HTTLPR gene polymorphism on antidepressant response to sleep depriva-


49. Benedetti F, Barbini B, Bernasconi A, et al. Lithium overcomes the influence of 5-HTTLPR gene polymorphism on antidepressant response to sleep depriva-

Keywords: anxiety disorder; depression; gene polymorphism; glutamate; inflammatory mechanism; neuroimaging; neuroplasticity
Les troubles de l’humeur et de l’anxiété sont caractérisés par un ensemble d’altérations de la morphologie et de l’activité cérébrales et par des perturbations neuroendocriniennes. La comorbidité entre anxiété et troubles dépressifs est particulièrement courante et présente des implications significatives en termes de présentation clinique, d’évaluation, de choix et d’efficacité du traitement, comme de l’évolution de la maladie, du pronostic et de l’évolution à long terme. Malgré cette comorbidité élevée, de nombreuses caractéristiques sont en faveur d’une classification où les troubles anxieux individuels restent à la fois distincts les uns des autres et distincts des troubles de l’humeur. L’hypothèse monoaminergique est le concept neurobiologique traditionnel de l’étiologie des troubles anxieux et dépressifs ; cependant, ces dernières années, l’attention des chercheurs s’est portée vers le glutamate. De plus, il devient évident que des facteurs autres que des déséquilibres entre les systèmes neurotransmetteurs doivent être pris en compte pour décrire une base neurobiologique de la dépression majeure en particulier, mais aussi des troubles anxieux ; il est maintenant bien connu que ces pathologies se caractérisent par une désynchronisation interne du processus de traitement de l’information induisant des altérations profondes de la structure, de la fonction et de la réactivité cérébrales. Les altérations ultérieures des mécanismes inflammatoires et de la neuroplasticité sont probablement impliquées dans la pathogenèse de ces troubles.
Almost all imaging techniques have evolved greatly, but many have not yet reached the stage whereby the strength of findings is guaranteed. In spite of caveats, neuroimaging has produced some important results; even if some or many of these will be contradicted by subsequent research, brain imaging is one of the investigative tools that has put psychiatric illness back where it is generated: the brain. This in itself has already been a worthwhile result.

Neuroimaging, be it based on emission tomography or magnetic resonance, has provided insight into brain changes associated with depression and anxiety, leading to further questions with regard to preclinical models and healthy volunteers. Not all findings, however, are consistent. Further investment is required toward the development of genotype and phenotype assessment in scanned subjects and toward increasing robustness of techniques, minimizing variation in results from one institute to another. Such variation in findings from different laboratories is likely to continue, as in some aspects of animal research, unless this investment occurs.

The advent of human brain imaging tools has allowed clinical neuroscientists to investigate brain processes and structures in vivo in a way that was unachievable 20-30 years ago. There are many tools to choose from that essentially use one of three technologies: emission tomography, magnetic resonance, and encephalography. Results from these investigations have extended psychiatric knowledge of brain function and dysfunction in anxiety and major depressive disorders. After an introduction that describes unresolved sources of possible confound, this review will briefly discuss the most important findings, in the author's opinion, in different domains. It will finally focus on describing results from molecular imaging as an example of why a detailed understanding of methodology and a complementary experimental medicine cycle are important. The last point is emphasized because if we achieve these, we are likely to build solid foundations that will allow us to draw strong conclusions about brain changes in psychiatric disorders. A thorough reading of neuroimaging in psychiatry reveals that for many key areas there are very different results from seemingly similar experiments. While authors can claim to have obtained similar results to other research groups, this is so because of a great deal of approximation. For all imaging, attention to methodological detail is very important as seemingly small technical and experimental variation can generate and explain very different results. Almost all imaging techniques have evolved greatly, but many have not yet reached the stage whereby the strength of findings is guaranteed. To this extent, we may have to consider a proportion of the results as preliminary. The most robust results seem to be the findings that confirm theories based on experimental animals, yet the true power of the techniques in the long term is likely to be the demonstration that not all human brain processes map directly on animal equivalents and that change secondary to human disease may not be a variation of changes observed with similar processes in health.
Furthermore, all the investigations are carried out in specialized centers and very unusual environments, which may have diverse effects on patients and healthy volunteers, potentially changing the ecological validity, nature, or magnitude of the observed parameters. Finally, it is likely that small variations in clinical characteristics of those taking part in experiments have the potential to alter results; sometimes these differences are not detected by experimental protocols and measuring instruments, losing “fine grain” information that may have explanatory power.

For example, most studies try to recruit people with “pure” syndromes, but how different are depressed people who do not have prominent anxiety symptoms from the equally prevalent depressed patients with comorbid anxiety disorders or subthreshold anxiety disorders? What are the differences between depressed people with overvalued guilt and reference ideas from patients who do not have these and from depressed people who have delusions of reference or guilt? How does prominent suicidal ideation change brain structure and function in depression and in anxiety disorders? Is suicidality a separate variable that should be teased out independently? If so, what is the boundary that would divide it from people who have no suicidal ideation? Is wishing to be dead truly different from having thoughts of killing oneself?

Finally, on a global scale, there are differences between nations, which are not only due to the diversity of any one sample or genetic background, but also to local socioeconomic factors. For example, does research carried out with patients from the public health sector produce the same results as research carried out in people who only get free health care if they take part in research?

In spite of the above caveats, neuroimaging has produced some important results: even if some or many of these will be contradicted by subsequent research, brain imaging is one of the investigative tools that has put psychiatric illness back where it is generated: the brain. This in itself has already been a worthwhile result.

**Anatomical brain mapping**

Anatomical magnetic resonance imaging (MRI) and magnetic resonance (MR) tractography can be used to measure anatomical variables. The former can measure gray and white matter and cerebrospinal fluid (CSF) distribution while the latter can measure the thickness and direction of white matter tracts that connect brain areas. Both rely on signals that are relative and where boundaries define categories, so variability is expected in the results from different centers using different scanners and analytical tools. In addition, while spatial “normalization” (the process of stretching any brain volume to make it fit with standard templates) is essential for volumetric comparisons, this does not fully avoid partial volume effects (whereby a signal is diluted and smoothed out at boundaries between structures); so caution has to be exercised when interpreting results, making certain that appropriate comparisons have been made.

While diffusion tensor imaging has so far not produced any significant findings in the field of anxiety and depression except for helping to separate the connective anatomy of some of the putative circuits, volumetric analysis has demonstrated that the hippocampus, amygdala, anterior cingulate, basal ganglia, and parts of the frontal cortex have smaller volumes in people with depression; ventricular space is also increased. This is consistent with neuropathological findings which have noted that with recurrent depression there is loss of brain tissue, and with resting metabolic studies which show a change in metabolism in some of the same areas. Of greatest interest is the fact that hippocampal atrophy seems reversible on successful antidepressant treatment or on cessation of the depressive episode. In the hippocampal area, this could be due not only to glial proliferation and synaptic enrichment, but also to neurogenesis.

Anatomical studies have also revealed that patients with major depression have increased white matter abnormalities, especially when older. The treatment implication of these findings is that people who have these vascular lesions may be harder to treat successfully and that medicines that increase an orthostatic drop in blood pressure may contribute to the problem. No such difference has been found for anxiety disorders, except for panic disorder where there is an increase in white matter abnormalities in the temporal lobes. Very similar brain areas have been implicated in morphological changes in anxiety disorders. However, the only disorder where a decrease in volume has been shown to be reversed by treatment is posttraumatic stress disorder, where hippocampal

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CFS</td>
<td>cerebrospinal fluid</td>
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<td>ECS</td>
<td>electroconvulsive shock</td>
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<td>ECT</td>
<td>electroconvulsive therapy</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;</td>
<td>γ-aminobutyric acid ionotropic receptor family A</td>
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<td>HMPAO SPECT</td>
<td>hexamethylpropyleneamine oxime single-photon emission computed tomography</td>
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<td>5-HT</td>
<td>5-hydroxytryptamine</td>
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<td>MAO</td>
<td>monoamine oxidase</td>
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<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
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<td>MEG</td>
<td>magnetoencephalography</td>
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<td>MR</td>
<td>magnetic resonance</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
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<tr>
<td>OCD</td>
<td>obsessive-compulsive disorder</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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volume increases with antidepressant treatment and is accompanied by improvements in specific memory tests. In addition, obsessive-compulsive disorder (OCD) seems to have a different pattern of volume changes from other disorders, whereby thalamus and basal ganglia have an increase in volume, and the anterior cingulate and the orbitofrontal cortex show a decrease in volume. These studies emphasize that some structural changes, eg, in the hippocampus, may be common to a number of psychiatric disorders while others, eg, basal ganglia, may help differentiation between disorders.

Functional brain mapping

Functional MR, MR arterial spin labeling, water or fluorodeoxyglucose positron emission tomography (PET), hexamethylpropyleneamine oxime single-photon emission computed tomography (HMPAO SPECT), electroencephalography (EEG), and magnetoencephalography (MEG) are used to investigate resting or task-related activity in populations of neurons. Understanding that the signal is generated by summation of hundreds of thousands of neurons is important as it can address apparent discrepancies in results when compared with invasive preclinical studies, whereby electrodes can be so accurate as to record the activity of single neurons in specific brain structures. Encephalographic techniques have very good temporal resolution, but poor anatomical resolution, while tomographic techniques have reasonable spatial resolution and poorer (MR) or very poor (PET/SPECT) temporal resolution. Some experiments now combine them in order to gain precision in the spatial and temporal domains.

Encephalographic techniques record the summation of electrical or magnetic neuronal signals through the skull. The other techniques use metabolic surrogate measures of multineuronal synaptic activity such as blood perfusion or tissue metabolic rate. The general assumption is that the local level of neuronal activity is highly correlated with glucose consumption (thus with fluorodeoxyglucose trapping) and/or with local perfusion; however, there have been a number of studies where recorded changes in local fluorodeoxyglucose concentration do not map on all the perfusion changes and vice versa, demanding that we better understand the nature of the signals. As well as transient localized changes, some of these techniques can measure the change in temporospatial correlation of activity from different brain areas at rest or during experimental or control conditions.

Initial and subsequent studies in depression have demonstrated decreases in activity in the dorsolateral prefrontal cortex, although this may be more closely related to symptoms of slowing and psychomotor retardation. The approach of trying to map individual symptoms has been less popular compared with those of investigating network changes with recovery, changes in emotion in healthy volunteers, and healthy volunteer–patient differences elicited by carrying out specific tasks in the scanner. The main finding associated with depression recovery has been alteration in function in the subgenual cingulate in response to physical treatments and placebo; this has not been a universal finding, but has been useful in developing a successful target for deep brain stimulation in treatment of refractory depression. In addition, this same area has been reported to be within the network implicated in the experience of sadness in healthy volunteers, lending further credence to its pivotal implication.

Changes in amygdalae reactivity to presentation of emotional faces has been used both as a marker of successful treatment and of early changes in brain function with antidepressants. Medial and dorsolateral frontal activation have also been found to be altered in a number of comparative experiments, including studies of response to social stimuli or to emotional distractors during a working memory task in remitted unmedicated patients, which could be trait abnormalities. Studies of functional connectivity suggest decreased connectivity between limbic structures and frontal areas, which may be more severe in treatment of refractory depression and which are consistent with the effects described in the previous three paragraphs. In anxiety disorders, key findings have been the overactivity of fronto-striatal-thalamic circuits in OCD and differences in amygdalae activity in social anxiety and panic disorder and posttraumatic stress disorder. These are emerging as differences which map across a number of different disorders and may be regarded as a future way to classify diseases.

Receptor, neurotransmitter, and transporter mapping

Other radioligand PET/SPECT and MR spectroscopy (MRS) measure the concentration of specific biochemical molecules. While MRS measures these directly, provided that adequate calibration of the instrument has been achieved, emission tomography relies on radioactive emission from appropriate "tagged" ligands to record changes in concentration of these molecules in various parts of the brain over a period of time. Since this signal represents the totality of the signal from a particular small volume of the brain (voxel), a number of assumptions have to be made in order to finally extract the signal of interest. These only work if the ligand has been administered in tracer doses, if vascular effects can be excluded, if an appropriate, robust and unconfounded reference measurement can be achieved to account for transport into the brain and for nonspecific binding, and if a temporary equilibrium has been reached. The main PET findings in terms of receptor/transporter changes in affective and anxiety disorders are summarized in Table I (page 286). SPECT findings are not summarized here, as for a variety of reasons they are more difficult to interpret.

As can be seen, there are a number of issues:

- To date relatively few brain receptors and transporters can be studied. This is because synthesizing PET compounds is
not very difficult, but finding ones that have the characteristics that allow signal recovery is very difficult. Useful brain PET ligands have to be able to cross the blood-brain barrier (i.e., be lipophilic) yet have relatively little nonspecific binding.

However, even with existing compounds, there have been a limited number of investigations. These studies are considered to be expensive and often require a considerable team effort. Only a few centers exist in the world that are able to carry out this work to a high standard and there has never been a combined and considerable industrial-governmental investment in the area, with some of the promising laboratories not managing to achieve sustainability.

Results can be contradictory; there are many potential reasons for this, some being the clinical presentation and state of the study sample, and some due to technical issues, discussed in part below.

For some ligands the interpretation can be twofold: for example, a decrease in tracer binding at the D2 receptor can occur because the density of receptors is decreased or because there is an increase in synaptic dopamine. In this respect, it is, for instance, interesting that D2 binding is unaffected in people who are currently experiencing hypomania. This may be true or an artifact because people who are likely to stay in the scanner must have a mild form of the disease or because the ligand measures the total of functioning and internalized receptors! Here I will discuss two examples that I think are conceptually important: receptor changes in anxiety disorders and 5-HT1A binding in depression.

The most intriguing finding in anxiety disorders is that when \( \gamma \)-aminobutyric acid ionotropic receptor family A (GABA<sub>A</sub>) benzodiazepine receptors have been measured, there are localized or even global decreases in receptor expression; in complementary studies, 5-HT<sub>1A</sub> binding is also decreased, and this can be partially reversible with drug response. When these findings are reviewed their importance is that they map to receptor knockout studies in mice, whereby underexpression of GABA<sub>A</sub> receptors or of 5-HT<sub>1A</sub> receptors leads to increases in anxiety and decreases in expression of the other receptor, a situation that can be replicated with increases in corticosterone and with other neurochemical phenomena associated with increased anxiety (see also discussion in reference 27). This is an important mapping of human findings on preclinical studies and vice versa, which has not yet been followed up to its full extent.

5-HT<sub>1A</sub> receptors are also thought to be important in depression and in mediating the cerebral effects of stress responses. Since the development of WAY-100635 as a ligand for PET studies, exquisitely delineating 5-HT<sub>1A</sub> receptors (Figure 1), the issue of 5-HT<sub>1A</sub> expression in depression has been studied by a number of groups. Until these studies, the only data available came from ex vivo measurement in patients who had undergone neurosurgery for intractable depression whereby both a decrease in \( B_{\text{max}} \) and \( K_d \) had been observed. The majority of reported PET studies showed a decrease in cortical and raphe binding in depression; however, one group at Co-
Foundations from studies of occupancy or in response to physical treatments (Table II) have demonstrated that MAO inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) achieve their effects at occupancies/binding above 70%-80% and that pindolol, which was studied as an antidepressant augmenter, did not achieve 5-HT1A occupancies that were high enough to consistently test the hypothesis that raphe 5-HT1A blockade would augment antidepressant response. In addition, one of these studies demonstrated that pindolol achieves different occupancies in the raphe and the cortex, a finding that is not easily explained given that pure antagonists do not do this. Unfortunately, this finding has never been further investigated in preclinical models, even though it may inform on serotonergic system regulation. Another interesting finding is that electroconvulsive therapy (ECT) downregulates 5-HT2 receptors in man, which is not what is seen with electroconvulsive shock (ECS) in rats, but is consistent with the effects in primates and its powerful antidepressant effects. These studies should be repeated across chemical systems to ensure that downstream effects of treatment are also well understood.

**Conclusion**

Neuroimaging remains an important and powerful tool in the investigation of human anxiety and depression. However, the findings need to be scrutinized with a critical eye and funding for this area should be made a priority so as to be able to obtain robust measures (thus far lacking) of brain function in disease. The apparent discrepancies are either due to unsophisticated clinical categorization or to methodological issues that will be resolved with time.

References


La neuro-imagierie, scanner ou IRM, a donné un aperçu des modifications cérébrales liées à la dépression et l’anxiété et a amené d'autres questions sur les modèles précliniques et les volontaires sains. Tous les résultats ne sont cepenchant phénoméne de sujet examinés ainsi que pour augmenter la fiabilité de certaines techniques, ce qui permettra de diminuer les variations entre les résultats d’un centre à l’autre. Sans cet investissement, il est probable que des laboratoires différents continueraient à produire des résultats hétérogènes, comme c’est le cas dans certains aspects de la recherche animale.
Anxiety disorders are some of the most common psychiatric disorders, and their risk factors are not fully understood. This review addresses the role of abnormal circadian rhythms in anxiety disorders; these abnormal rhythms may explain some symptoms or highlight the way some risk factors may increase the risk of later anxiety disorders. The presence of a pathological sleep-wake cycle in anxiety (due to sleep difficulties in many anxiety disorders), for example, demonstrates that one of the most frequent symptoms is linked to circadian rhythms. As anxiety is often viewed as a developmental disorder, it is interesting that some cohort studies demonstrated that greater regularity in newborns enhances the quality of care provided by the parents, which in turn lowers anxiety symptoms. The synchronicity between child and parent is important, as demonstrated by lower maternal stress reducing stable inhibition temperament, a marker that has been associated with later risk of anxiety disorders. For some of these cohort studies, cortisol levels were also measured, and abnormal cortisol circadian rhythm was proposed as a mediating factor between early stress and later anxiety disorders. Some studies also analyzed different candidate genes in anxiety disorders and found significant association with two interesting clock-related genes. Indeed, the DRD2 gene was shown to be induced by light in the retina and was also strongly associated with anxiety disorders. Although the literature reviewed herein is largely unspecific, it is hoped that the existence of an antidepressive treatment (agomelatine), which acts through melatonergic and 5-HT_{2C} receptors, and which has now demonstrated strong efficacy on anxiety within depression, will enhance this type of study.

Anxiety disorders are some of the most common psychiatric disorders, with a 12-month prevalence reported to be 18.1% in the US population. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), defines 12 types of anxiety disorders that can be grouped under the following headings according to their symptom profiles: panic disorder (PD) with or without agoraphobia, phobias including specific and social phobias, obsessive-compulsive disorder (OCD), stress disorders including posttraumatic stress disorder and acute stress disorder, generalized anxiety disorder (GAD), anxiety disorders due to known physical causes, and anxiety disorder not otherwise specified. Experience of distress with accompanying disturbances in sleep, concentration, and social or occupational functioning are common symptoms in many of the anxiety disorders. Indeed,
anxiety disorder patients often suffer from sleep disturbances constituting diagnostic criteria of posttraumatic stress disorder and GAD. Also, PD has been associated with sleep disorders.

**Symptoms of anxiety reflecting abnormal circadian rhythms**

The biological clock of mammals (the suprachiasmatic nucleus [SCN]) controls a variety of behavioral rhythmic phenomena, such as locomotor activity and sleep-wakefulness, apart from secretion of various hormones. Therefore, sleep complaints are pertinent to circadian rhythms.

Interestingly, sleep complaints may also be considered a risk factor, and among the most robust prodromal symptoms reflecting anxiety disorders. Indeed, according to two follow-up studies presence of sleep disorder at time 1 (with no psychiatric disorder) was associated with a higher risk of anxiety disorder at time 2, from one year to three years later. More precisely, the epidemiological study based on young adults showed that having pure insomnia at the first visit increased by two the risk of having any anxiety at the second visit (95% confidence interval [CI] of the odds ratio [OR] = 1.08-3.60).

Sleep definitely reflects a core aspect of circadian activities of subjects, but sleep difficulties only represent one facet of circadian activities in patients with anxiety disorders, and is largely shared with other psychiatric disorders such as mood disorders. Knowing if anxious patients have more abnormal social rhythms than healthy controls is therefore much more interesting. Patients with anxiety might indeed be more sensitive to life changes which result in disruption of daily routine, as these patients were considered as relying more than others on familiarity, predictability, and controllability to manage their lives. High levels of anxiety can indeed be disorganizing and disruptive of daily rhythms because of impaired coping and problem solving ability, which might increase the disruptive effects of life events on the regularity of everyday activities. A reduced exposure to zeitgebers (time-giving cues) could be proposed as an alternative explanation, phobic avoidance, for example, being a common strategy in anxiety disorder to lower the level of exposure to stress, but which also reduces exposure to zeitgebers.

Shear et al compared 48 patients with an anxiety disorder (and no comorbid depressive episode) with 41 controls, assessing regularity of daily activities according to a two-week daily monitoring with the Social Rhythm Metric (SRM). Anxiety disorder patients reported lower rhythmicity of daily life activities and significantly lower frequency of activities than controls. The distinctions between lowered intrinsic rhythmicity in daily activities or heightened vulnerability to stimuli which disrupt social rhythms are difficult to assess in such a study.

Considering abnormal circadian rhythms to be important factors in anxiety disorders does not only require that sleep disorders are both associated with and risk factors for anxiety and that patients with anxiety disorders have abnormal social rhythms. It also requires an explanation of how such abnormalities relate to the onset of anxiety disorders. Therefore, developmental approaches, genetic analyses, and further understanding of the involved biological mechanisms are expected to shed light on such a hypothesis.

**Early development: from rhythmicity and inhibition to anxiety**

How circadian rhythms might lead to psychiatric disorders such as mood and anxiety disorders, when they are running according to inappropriate timing or in an irregular fashion, is a matter of debate.

Because parents are adults with well-developed daily behavior patterns, an infant’s level of circadian regularity will determine the nature of his or her interaction with them, and may thus affect early attachment relationships and the development of self-regulatory social skills in infancy. Greater infant sociability is indeed positively related to maternal contact and responsiveness from 1 to 9 months, and secure infant attachment predicts lower levels of child and adolescent anxiety disorders. A “virtuous” circle (Figure 1) would take into account that stronger and more regular circadian rhythms in the infant may increase the predictability of infant demands, leading to enhanced parental perception of need cues and increased parental confidence which might further strengthen caretaking routines. Indeed, mothers and fathers, whose infants exhibited significant increases in regulation and predictability from age 3 to 9 months, displayed increased sensitivity during play and greater caretaking involvement.

Temperamental rhythmicity in children directly refers to the predictability or unpredictability in timing of the sleep-wake cycle, hunger, feeding, and elimination. Difficult or dysregulated temperament has been associated with greater risk for psychopathology, including symptoms of anxiety. Children high

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**Selected abbreviations and acronyms**

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BCL2</td>
<td>B-cell CLL/lymphoma 2</td>
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<tr>
<td>DRD2</td>
<td>dopamine receptor D2</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</td>
</tr>
<tr>
<td>PD</td>
<td>panic disorder</td>
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<tr>
<td>OCD</td>
<td>obsessive-compulsive disorder</td>
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<td>GAD</td>
<td>generalized anxiety disorder</td>
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<td>SRM</td>
<td>Social Rhythm Metric</td>
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<td>SCN</td>
<td>suprachiasmatic nucleus</td>
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<tr>
<td>PAWR</td>
<td>PRKC, apoptosis, WT1, regulator</td>
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<tr>
<td>PVN</td>
<td>paraventricular nucleus</td>
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<td>AVP</td>
<td>vasopressin</td>
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in effortful control exhibit lower levels of internalizing symptoms, such as anxiety. Thus, an infant’s ability to direct attention may represent greater self-regulation, and is perhaps associated with stronger and more regular circadian rhythms.

In order to more specifically test the idea that babies with less predictable rhythms could be at risk of anxiety, Monk et al. assessed the rhythms of 59 1-month old babies. They were then followed up for up to 13 years, assessing the level of anxiety according to the MacArthur Health and Behavior Questionnaire. The Baby SRM score was significantly correlated with school-age anxiety symptoms, with higher (more regular) SRM scores associated with lower overall level of anxiety symptoms, across the five separate time points (age 6, 7, 9, 11, and 13 years, r = -0.35, -0.37, -0.24, -0.26, and -0.30, respectively). There was no significant correlation of Baby SRM with child depression. More precisely, the initial Baby SRM explained between 12% and 22% of the total variance of the anxiety level that was observed at up to 13 years old. Thus, daily behavioral regularity in the life of a 1-month old infant appears to be predictive of anxiety levels more than a decade later.

Biological markers of circadian rhythms and their relevance in anxiety

One candidate biological marker of anxiety and circadian rhythms is elevated activity of the limbic system, as testified by elevated cortisol levels, which is associated with the generation of fear in children. There are multiple pathways that control the timing and shape of cortisol rhythms, from the SCN to the paraventricular nucleus (PVN) as well as direct input from the SCN to the adrenal cortex. Imaging studies in monkeys and humans suggest that individual differences in limbic system activity (including the amygdala) are associated with temperamental inhibition and anxiety-related behaviors. Inhibition is linked with physiological reactivity across systems regulated by the central nucleus of the amygdala, including the neuroendocrine response system. Of particular interest are findings suggesting that increased pituitary-adrenal activity, assessed by salivary cortisol levels, is associated with extreme childhood inhibition.

Monkeys exposed to early environmental perturbations and negative maternal behaviors tend to develop increased hypothalamic-pituitary-adrenal reactivity and stable fear-related behaviors. Studies of young children also suggest that maternal behaviors, including being overly solicitous as well as negative behaviors (eg, low engagement, hostility) associated with maternal depression or distress, might influence the development of elevated cortisol levels and early inhibition.

A prospective study was conducted in 1-month old infants to 14- to 15-year-old teenagers to test the role of cortisol release as an intermediate factor between parental distress and their children’s later anxiety disorders. In this cohort, initial level of inhibition (according to a videotaped observation of a 2-hour home visit) and afternoon basal cortisol were compared with later levels of inhibition and presence of DSM-IV diagnoses (with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version). Chronic high levels of inhibition were significantly associated with a lifetime history of social anxiety disorder by grade 9. A “stress pathway” was identified, highlighting that children exposed to greater maternal stress beginning at birth are at greater risk for developing chronic high inhibition, in part because they experience increased afternoon cortisol levels as preschoolers. The role of cortisol as a biological marker of later risk of anxiety disorder is additional proof of the link between anxiety and circadian rhythms.

Another study attempted to bridge the gap between anxiety traits and daytime cortisol on the one hand and early abuse on the other. Among the array of difficulties exhibited by maltreated children, especially for very young ones, one of the most...
Anxiety disorders and circadian rhythms – Gorwood

Prevalent and widely documented is indeed an increased risk for internalizing problems, including anxiety disorders.31 In this study, during summer camp, 265 school-aged maltreated children and 288 non-maltreated children were compared with regard to morning and late afternoon cortisol levels on five consecutive days. Children experiencing early physical and sexual abuse with high internalizing symptoms uniquely exhibited an attenuated diurnal decrease in cortisol, indicative of neuroendocrine dysregulation. Therefore, dysregulation of cortisol could distinguish a subgroup of patients who have a significant risk factor (early sexual abuse) and who already have some anxiety features (high internalizing level), reinforcing the idea that hormones with circadian variability could be involved in the onset and the development of anxiety disorders.

Early exposure to a range of risk factors, such as poor secure relationship with the parents and early sexual abuse, has thus been demonstrated to have an important role in the risk of anxiety disorders. The concept of exposure might be particularly important in the organization of circadian rhythms. Indeed, the perinatal photoperiod has lasting effects on behavior and the circadian rhythms expressed by clock neurons, and it determines the responsiveness of the biological clock to subsequent changes.32

Furthermore, in humans, cortisol (associated with wakefulness) and melatonin (a hormonal signal related to anticipated onset of sleep in diurnal animals) appear to act in opposite manners to each other, both functionally and at the neuro-anatomical level. An interesting hypothesis has been put forward, proposing that the interdependence between cortisol and melatonin in relationship to different psychiatric disorders may be more important than either of their independent relationships to the sleep-wake cycle.33 How could such an interaction between melatonin and cortisol occur? Vasopressin (AVP) receptors are located on the SCN;34 their activation by cortisol is thus expected to affect the release of melatonin. Another possibility lies in the effect of melatonin on cortisol as hypertrophy of the rat adrenal and pituitary gland is observed after pinealectomy, which suggests that melatonin may help suppress the hypothalamic-pituitary-adrenal axis.35

Nevertheless, biological markers might be associated with the presence of the disorder, rather than testifying to a specific type of vulnerability. The biological markers protected from this bias are genetic markers.

Genetics
Anxiety disorders are complex diseases; twin and family studies have provided evidence for both genetic and environmental factors affecting predisposition. On the basis of the meta-analyses conducted by Hettema et al.,36 the estimated heritability of PD and GAD was assessed as ranging between 30% and 45%. Other anxiety disorders aggregate in families as well. A more recent approach on the heritability of anxiety disorders relied on a latent liability to all anxiety disorders. Such a factor had a higher heritability (54%) than each disorder (23% to 40%), most of the genetic effect being common. Genes contributed over 50% to the covariance between liabilities.37 Therefore, the genetics of anxiety disorders may also help us understand whether anxiety disorders result from an abnormality in circadian rhythms.

Recent isolation of different mammalian homologues of clock genes and their circadian expression in the SCN suggests that molecular components and some mechanisms of the mammalian circadian clock are evolutionarily conserved. Therefore, animal studies on clock genes are informative.

Mice carrying a mutation in the Clock gene were studied for their overall behavioral anxiety profile, according to the open field and elevated plus maze paradigms. Both tests measure the amount of time spent in an anxiety-provoking space, such as the middle of an open field or unprotected arm of a raised platform, and both are sensitive to treatment with anxiolytic drugs. These results showed that the Clock mutants are less anxious or fearful than their wild-type littermates.38 However, as these mice also showed behaviors associated with mania, it is unclear how to best classify this phenotype.39 Another study40 showed that the expression of mPer1 mRNA was rapidly reduced in the cerebellum by acute intraperitoneal injection of anxiolytic medications (diazepam, triazolam and tandospiron), but not by clozapine and haloperidol, suggesting that altering circadian-clock–related gene levels could theoretically contribute to the therapeutic action of these drugs.

These two studies provide very indirect evidence for the role of clock genes in anxiety disorders in human. The only study in human we are aware of tested 13 circadian-clock–related genes in a sample of 321 individuals diagnosed with an anxiety disorder and 653 matched healthy controls with a relatively homogeneous ethnic background (all of Finnish origin).41 Evidence for association was detected for three of these genes (BCL2, DRD2, and PAWR) belonging to the signaling pathway connecting circadian rhythmicity and anxiety-like behavior (Table I).41

DRD2 is particularly interesting, as it is also induced by light in the retina42 and was previously associated with neuropsychiatric disorders largely overlapping anxiety disorders, such as alcoholism with comorbid anxiety,43 neuroticism-anxiety personality trait,44 posttraumatic stress disorder,45,46 and social phobia.45 Clock genes constitute a large number of candidate genes to explain abnormal circadian rhythms in anxiety disorders.2

Conclusions
Research directly devoted to the relationship between anxiety disorders and circadian rhythms is surprisingly poor, probably as the circadian variability in anxiety disorders is less ob-
vious than in mood disorders. But restricting to this purely observational assumption might be disadvantageous, as we still lack important insight enabling detection of new pathways explaining anxiety. Furthermore, the recognized role of circadian rhythm abnormalities in major depressive disorder should reinforce the need to assess this domain in anxiety disorders, as anxiety and depression have more shared than specific risk factors.

Although the literature only offers indirect evidence, it is particularly interesting that some of the core risk factors—such as early physical and sexual abuse, insecure attachment, and vulnerability genes—for many anxiety disorders, have the potential to explain abnormal circadian rhythms. For example, and in accordance with the developmental theory of anxiety disorders (ie, that anxiety disorders are acquired early in life), it is particularly interesting that even perinatal variations of the photoperiod have lasting effects on the circadian rhythms expressed by clock genes. Aside from this developmental aspect of the disorder, two genes have been associated with anxiety and may also shed light on its circadian aspect. One of these, the DRD2 gene, which might have a key role in the reward process, was associated with different anxiety disorders as a clock-related gene. Furthermore, an antidepressive treatment (agomelatine) with a mechanism of action involving melatonergic receptors and 5-HT2C has now demonstrated strong efficacy on anxiety in depression and will hopefully enhance studies like these.

**References**

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**Table 1. Association of different genetic polymorphisms of circadian clock-related genes with various phenotypes of anxiety-related phenotypes.**

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Gene</th>
<th>SNP</th>
<th>Allele</th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorder broad</td>
<td>DRD2</td>
<td>rs4245146</td>
<td>C</td>
<td>0.77</td>
<td>0.70</td>
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<td>0.45</td>
<td>0.003</td>
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<tr>
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<td>G</td>
<td>0.71</td>
<td>0.59</td>
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</tbody>
</table>


Keywords: anxiety disorder; circadian rhythm; clock-related gene; cortisol; melatonin; rhythmicity

Troubles anxieux et rythmes circadiens

Les troubles anxieux font partie des troubles psychiatriques les plus courants et leurs facteurs de risque ne sont pas entièrement compris. Cet article aborde le rôle des rythmes circadiens anormaux dans les troubles anxieux qui pourraient expliquer certains symptômes ou souligner la façon dont des facteurs de risque peuvent augmenter le risque de troubles anxieux ultérieurs. Par exemple, la présence d’un cycle pathologique veille-sommeil dans l’anxiété (due aux troubles du sommeil présents dans beaucoup de troubles anxieux) montre que l’un des symptômes les plus fréquents est lié aux rythmes circadiens. L’anxiété étant souvent considérée comme un trouble du développement, il est intéressant de constater que certaines études de cohorte ont montré qu’une meilleure régularité du sommeil des nouveau-nés améliore la qualité des soins parentaux, ce qui diminue en retour les symptômes anxieux. La synchronisation entre parents et enfants est importante comme le montre le fait qu’un état de stress maternel plus faible diminue le tempérament d’inhibition comportementale stable, qui est un marqueur associé à un risque de troubles anxieux ultérieurs. Certaines de ces études de cohorte ont mesuré les taux de cortisol et ont proposé un rythme circadien anormal de cortisol comme facteur de liaison entre un stress précoce et des troubles anxieux ultérieurs. Des études ont analysé différents gènes candidats dans les troubles anxieux et ont trouvé une association significative avec deux gènes de l’horloge intéressants. En effet, le gène DRD2 est activé par la lumière dans la rétine et fortement associé aux troubles anxieux. Bien que la littérature passée en revue dans cet article ne soit pas très précise sur ce point, on peut espérer que l’agomelatine (traitement antidépresseur), qui agit sur les récepteurs mélatoninergiques et les récepteurs 5-HT2C et qui a montré une bonne efficacité sur l’anxiété des troubles dépressifs, puisse améliorer ce type d’études.
While study of the mechanisms and actions of antidepressants has embraced cognitive theory, cognitive theory has increasingly embraced neuroscience. The increased availability of brain imaging modalities has allowed cognitive science to be based simultaneously on observing behavior and on observing brain function; this has transformed attitudes in psychology. This fertile environment may foster new ideas that bridge the biological and cognitive narratives of depression.”

Emotional blunting in anxiety and depression: neurobiology and psychopathology

by G. M. Goodwin, United Kingdom

Approaches to understanding anxiety and depression have been polarized between the neurobiological and the psychopathological. These alternative narratives to explain the same phenomena of anxiety and depression have given rise to competing approaches to treatment based on medicines and psychotherapy, respectively. They have long demanded unification and in recent years significant convergence between the two has been made possible by the development of cognitive neuroscience. This has been based on the analysis of cognition and its neural underpinning as revealed by human functional imaging. Both depression and anxiety are characterized by emotional biases. In depression, there is often an apparent blunting of positive emotional experience; in anxiety, fear and threat experiences may be magnified. It is now possible to analyze antidepressant drug effects in terms of the cognitive biases associated with the processing of emotionally relevant information in perception or memory. And the mechanisms underlying retraining or exposure in cognitive behavior therapy can be analyzed with reference to the underlying neural changes. One consequence of this, as will be shown here, is the new understanding that, just as antidepressants have the surprising effect of treating depression, a disorder of the emotions, it is possible that the serotonergic treatments may also give rise to emotional blunting. This was originally based on clinical observation, but with appropriate scales and double-blind designs, antidepressants may be differentially implicated in the effect. The emphasis on mechanisms of emotional processing, rather than simple phenomenology, offers novel ways of approaching how emotions are blunted in depression, and to what extent this is a fundamental feature of depressed mood and its remission.

Medicographia. 2012;34:295-299 (see French abstract on page 299)

For many years, approaches to understanding anxiety and depression have polarized somewhat between the neurobiological and what might imprecisely be called the psychopathological. These alternatives are effectively narratives to explain the same phenomena of anxiety and depression. But they have given rise to competing treatment traditions unduly focused on medicines on the one hand, and psychotherapy on the other. They have long demanded unification, but have lacked common ground on which to effect a rapprochement. Very recently, significant convergence between the two has been made possible by advances in cognitive neuroscience. One consequence of this, as will be shown here, is the new understanding that, just as antidepressants have the surprising effect of treating depression,
a disorder of the emotions, it is possible that drugs may also give rise to emotional blunting. Furthermore, the traditional pragmatic emphasis on symptoms has shifted towards the effects of mood disorder and anxiety on emotional processing.

The neurobiological model

Neurobiological approaches to depression and anxiety take their origins from the clinical research that proved the effectiveness of treatments like the tricyclic antidepressants and the benzodiazepine anxiolytics. Because these medicines were effective—and in the case of the antidepressants perhaps most effective—in patients with the most severe illness, they provided an obvious starting place for biological accounts of the underlying neural basis for mood and anxiety disorder. The ideas that developed through the 1960s and subsequently were based on the seminal finding that the tricyclic antidepressants were reuptake inhibitors for the neurotransmitters serotonin and noradrenaline (and to a lesser extent dopamine). These transmitter systems seem to possess many of the properties that one might expect in a system regulating just those global changes in behavior and experience that characterize depression or normal mood. Thus, they were demonstrated to fulfill regulatory roles in sleep, sexual function, appetite, and attention. Disorders of function in all these domains are obvious in patients with depressive episodes; therefore, the idea that these symptoms are the consequence of changes in neurotransmitter levels or overall system function was for many years attractive and heuristic useful in generating innovative drug development. Independent clinical research showed that a different class of drugs, inhibitors of monoamine oxidase (MAO), also possessed antidepressant and anxiolytic properties. The convergence of therapeutic effect between the reuptake inhibitors on the one hand and the MAO inhibitors on the other seemed to confirm that the monoamine systems would be the locus for the neurobiology of depression and potentially also anxiety. Drug innovation focused on trying to produce more acceptable versions of the original classes of antidepressant drugs and so we now have drugs selective for reuptake systems of serotonin and noradrenaline, and reversible enzyme inhibitors for the MAO enzyme subtypes, all less toxic in overdose.

Had depression or anxiety been a monoamine disorder in the sense that Parkinson's disease is a dopamine disorder, then both the anatomy of any pathology and the biochemistry of the relevant neuronal systems should have been obviously disturbed. In fact, it turned out that this was not correct. It was difficult to demonstrate large and invariant changes in the metabolism of the relevant neurotransmitters in the functional neuropathology of depression. In so far as there is a consensus about what the postmortem data shows, it is really focused on changes in synaptic proteins in the cortex, and these are most evident in patients with bipolar disorder. A purely neurobiological formulation of depression etiology, inferred from treatment effects, therefore ran into a disappointing cul-de-sac. Indeed, this failure to demonstrate any convincing fit between the monoamine transmitters and the pathology of the condition exhausted its heuristic potential and the consequence has been wholesale disinvestment by Big Pharma from psychiatry, largely because the science of new discovery has proved so difficult beyond the monoamines.

The psychopathological or cognitive model

Throughout this era, the alternative narrative associated with clinical psychologists and their approach to the treatment of depression and anxiety with cognitive behavior therapy (CBT) has gained substantial support. The cognitive model of mood disorder stemmed from the seminal ideas of Aaron Beck. Having been brought up in the prevailing tradition of psychoanalysis in the United States, which stressed the unconscious causes of psychopathology, Beck’s insight was to ask very simply whether conscious cognitive distortions might underlie and maintain the states that we recognize clinically as depression and anxiety. In the case of depression, he proposed a triad consisting of negative views of the self, the world, and most particularly, the future. Beck took this to characterize all depressions regardless of the apparent clinical subtype, and moreover he proposed that the degree of negative thinking related directly to the noncognitive symptoms of depression such as sleep disturbance, etc. In its origins, this was not a theory of causation of depression, but a theory of how depression might come to be maintained and how therefore it might be reversed with a therapy that emphasized a correction of these cognitive biases.

CBT is intended to change how you think and what you do. It was strongly developed on the basis of formal cognitive theories of emotion and its regulation, and its evaluation was both more rational and more scientific than psychodynamic therapies had been. However, it never concerned itself very much with whether it had an underlying biological basis. Instead, it provided a pragmatic rationale to the psychotherapy which allowed treatment innovation, but within a closed high-level theory separate from brain function. This separation was reinforced by widely held views in psychology that the mind was really best addressed without reference to the brain. Until recently, this had largely remained unchallenged and CBT has, like antidepressant medication, run into some of the same limits to innovation, at least it has seemed so to a noninvolved observer such as myself.

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CBT</td>
<td>cognitive behavior therapy</td>
</tr>
<tr>
<td>LEIS</td>
<td>Laukes Emotional Intensity Scale</td>
</tr>
<tr>
<td>MAO</td>
<td>monoamine oxidase</td>
</tr>
<tr>
<td>ODQ</td>
<td>Oxford Depression Questionnaire</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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The application of neuroscience

The study of the emotions using the methods of neuroscience has generally lagged behind the investigation of other brain functions. The idea that the brain represents emotional aspects of external stimuli in particular brain areas is nevertheless an old one and has long emphasized the role of limbic cerebral cortex and associated subcortical structures such as the striatum, amygdala, and thalamus in providing the neural basis for the emotional world of animals and man. For example, our understanding of fear circuits in animals has been well advanced for many years, but has been slow in finding translation to understanding clinical anxiety in neurobiological terms.5,6 Given the emphasis on the amygdala as a key structure, it was not surprising that imaging studies in patients with anxiety showed enhanced processing of fear stimuli (e.g., fearful faces), even with subliminal stimuli.6 Findings in depression have generally been less consistent in demonstrating simple biases in emotional processing, despite the overwhelming clinical evidence for negative biases at a conscious level. In part, this will reflect at a behavioral level the impact of global impairments of memory and executive function that make depressed subjects difficult to test.6

Over 10 years ago, Catherine Harmer and I started to look at what effects antidepressants have on emotional processing, first in healthy volunteers and subsequently in patients.10,11 The findings have been surprisingly consistent in demonstrating that selective serotonin reuptake inhibitors (SSRIs), for example, reduce the capacity of individuals to detect negative emotion in the faces of others, increase the access to positive as compared with negative self-referential words, and reduce fear-potentiated startle responses. These findings allow a reformulation of how antidepressants may actually work, which can explain both their potential limitations and also why the biological changes that are seen in depressed states are not simply expressions of abnormal monoamine biochemistry.

The critical hypothesis is that antidepressants can change emotional bias, which is determined by relatively subtle alterations in function in the monoamine systems. On this view of drug treatment, what is most critical about a patient when depressed could be the extent to which they show automatic biases in their processing of emotional stimuli and the extent to which, when once these are reversed, recovery can then occur spontaneously.12 The critical feature, of course, is the link between a drug effect and a cognitive/emotional effect which is essentially automatic. However, emotional bias appears to be the target both for drugs, via automatic processing effects, and CBT, via its explicit focus on conscious emotional bias.

While study of the mechanisms and actions of antidepressants has embraced cognitive theory, cognitive theory has increasingly embraced neuroscience. The increased availability of brain imaging modalities has allowed cognitive science to be based simultaneously on observing behavior and on observing brain function; this has transformed attitudes in psychology. This fertile environment may foster new ideas that bridge the biological and cognitive narratives of depression. Imaging patients who have received cognitive therapy or volunteers who are studied while making emotional judgments has suggested a critical link between the automatic processing of emotional signals in the amygdala and the regulation of this activity from the frontal cortex.13 These top-down mechanisms are increasingly seen as the likely target for psychologically orientated therapies. On this view, therapy can strengthen this control by retraining habits and biases.14

This unified view of treatment efficacy, implicating neurobiological changes due to both drug action (on automatic processing mechanisms) and cognitive therapy (on the more voluntary aspects of cognitive control) is likely to be increasingly fruitful in the future. It invites a much closer examination of the extent to which drug treatments can facilitate psychological interventions and vice versa.

While this argument has been developed in relation to depression, it is just as likely to apply to anxiety as well, where psychological and drug interventions are both well developed. In relation to anxiety, the model of fear-potentiated startle can be used translationally in both animals and healthy volunteers.15 Thus, the potentiation of startle responses to distressing emotionally charged images is reduced by citalopram, but not by reboxetine, suggesting a greater potential efficacy for SSRIs in anxiety indications.12 Just as for major depression, the independent impacts of psychological training and drug treatment have the potential to inform treatment mechanisms in man.

Antidepressants and emotional blunting

This fusion of two previously disparate fields has thrown up a further question of remarkable interest, which is whether antidepressants themselves may actually lead to what is essentially emotional blunting. This was first proposed for patients who complained of reduced sexual interest while receiving treatment with SSRIs for depression. The data came from the Laukes Emotional Intensity Scale (LEIS),16 a self-report instrument comprising 18 questions to rate as compared with one’s “usual” state along a 5-point scale (a lot less/somewhat less/same as usual/somewhat more/a lot more). Significant reductions occurred in 12 of the 18 items, including ability to cry, irritation, care about others’ feelings, sadness, erotic dreaming, creativity, surprise, anger, expression of their feelings, worry, sexual pleasure, and interest in sex.16 It was suggested that antidepressants blunt not only sexual experience and interest, but also other aspects of emotional experience and behavior. While this is a very interesting hypothesis, these data did little to confirm it, because the discriminating items overlapped very obviously with what might have been residual symptoms of depression.
While an impact on sexual function could be formulated in terms of reduced function of relevant innervation in the sex organs and brainstem, any effect on the emotions might be expected to be more central within the brain. In any case, although the phenomenon of emotional blunting by SSRIs seems to have accorded very well with the experience of clinicians, it has been little investigated in the subsequent decade. When we reopened the question three years ago, there was no adequate scale with which to capture the experience which had been imputed. We therefore undertook a qualitative analysis of what patients actually complained of, a detailed inventory of what complaints were most frequent, the design of a scale to capture this experience, and its testing under conditions where patients would be blind to their treatment. This program has been, in part, motivated by the hypothesis that the new antidepressant agomelatine would lack the impact on emotional experience of the SSRIs. It is ongoing, but the results so far are thought provoking. They pose the central question of whether emotional blunting is simply a drug side effect, or an untreated aspect of depression, or some interaction between the two.

Our qualitative investigation of patient experience generated four dimensions. The four dimensions were “not caring,” “emotional detachment,” “reduction in positive emotion,” and “general reduction in emotions.” Several of the dimensions are highly correlated with depressive symptoms and so one would predict would be sensitive to depression. Indeed, they provide an alternative emotionally relevant depression scale, which we may call the Oxford Depression Questionnaire or ODQ. The development of the scale is still in progress. However, the performance of some of the items has been examined under double-blind conditions during the treatment of patients in a major depressive episode with either agomelatine or escitalopram. The findings are preliminary because the patient numbers were relatively small (the trial had already started when the study was added to it and the scale was only available for English-speaking patients). Figure 1 shows the findings for one of the most interesting of the items and poses key questions about the relationship between depression itself and the scale items and the response after treatment with different antidepressants.

Our provisional conclusions are that emotional blunting is a real effect and that it is more likely to occur when patients are taking a selective serotonergic drug than when they are taking agomelatine. Agomelatine does not increase the availability of serotonin in the brain, and the implication is that emotional blunting is a serotonergic side effect. What is not decided is whether such effects are nevertheless related to depression, which is a possibility as emotional blunting is a marked feature of being acutely depressed. This is illustrated by the baseline responses to the statement “My emotions lack intensity” in Figure 1: the percentage of patients endorsing this item implies a very common experience in major depressive episodes. With treatment with either an SSRI, escitalopram (10-20 mg), or agomelatine (25-50 mg), this rate falls as would be expected for a simple symptom of depression. At week 24 however, about twice as many patients continued to endorse this item in the escitalopram group as in the agomelatine group, despite equivalent remission on the Hamilton ratings (see legend, Figure 1). This is the first, albeit preliminary, double-blind evidence for a blunting effect of an SSRI, but it is also ambiguous because of the high baseline levels. The raised levels at week 24 could be a delayed effect of the SSRI per se or an aspect of the depressed state poorly treated by an SSRI. This raises the question addressed in the next paragraph.

![Figure 1](https://example.com/figure1.png)

**Figure 1. Patients endorsing the statement, “My emotions lack intensity.”**
Percentage of patients (n=66) endorsing the statement at baseline (W0), and after 2, 12, and 24 weeks (W2, W12, W24) of treatment with either agomelatine (blue) or escitalopram (light red). Mean Hamilton scale scores at W24 were 6.1±5.6 (median 4) for agomelatine- and 6.1±4.0 (median 4) for escitalopram-treated groups.

**Abstract P02-24.**

**Does emotional blunting occur in healthy volunteers who take SSRIs?**
The first studies of antidepressant effects in healthy volunteers were short-term and subjects showed no changes in mood and complained of no marked side effects. However, it is possible that with longer treatment periods, some of the effects on emotional processing would translate into emotional blunting. The basis for saying this is that the primary effect of SSRI treatment in several tests was to reduce the processing of negative stimuli, rather than to increase the salience of positive stimuli. This was seen for the perception of negative emotion in faces, both behaviorally and when imaging neural activity in the region of the amygdala. In behavioral experiments, agomelatine had no impact on the perception of negative facial expressions, except sadness. This approach has been supplemented in related studies, where, again in healthy volunteers, the SSRI citalopram reduced activation to positive appetitive stimuli in the ventral striatum and the ventral medial/orbitofrontal cortex, whereas the noradrenergic reuptake inhibitor reboxetine did not. Citalopram decreased neural responses to aversive stimuli more than did reboxetine. Treat-
ment of depression may be conceptualized as decreasing punishment signals and increasing reward. SSRIs appear to achieve the former more effectively than the latter and there- in may lie their potential for blunting emotional experience. These experiments were short-term and there were no subjective changes in the rating of pleasant and unpleasant stimuli by healthy volunteers. However, it is an open question whether, under these changed neural processing biases, an experience of reduced emotion might become more marked. The pre-
diction would be that this effect would only occur with serotonergic medicines and not with drugs acting like agonela- rine and reboxetine through nonserotonergic mechanisms.

Acknowledgment. Dr Goodwin holds grants from Baily Thomas, the Medical Research Council (MRC), the National Institute for Health Re- search (NIHR), Servier, and the Wellcome Trust, and has advised or re- ceived honoraria from AstraZeneca, Bristol Myers Squibb (BMS), Boehringer Ingelheim, Cephalon/Teva, Janssen-Cilag, Eli Lilly, Lundbeck, Otsuka, P1Vital, Pfizer, Roche, Servier, Schering Plough, and Takeda.

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Keywords: antidepressant; emotion; emotional blunting; major depression; side effect

ÉMOUSSEMENT ÉMOTIONNEL DANS L’ANXIÉTÉ ET LA DÉPRESSION : NEUROBIOLOGIE ET PSYCHO PathOLOGIE
La compréhension de l’anxiété et de la dépression a été abordée par deux approches opposées : la neurobiologie et la psychopathologie. Ces différentes manières d’expliquer les mêmes phénomènes d’anxiété ou de dépression ont entraîné la mise en concurrence d’approches thérapeutiques basées respectivement sur la médecine et la psycho- thérapié. Une unification est nécessaire depuis longtemps et le développement récent des neurosciences cognitives a permis une convergence significative entre les deux domaines. Ceci se fonde sur l’analyse de la cognition et de ses causes neurales par l’imagerie fonctionnelle chez l’homme. La dépression et l’anxiété sont toutes deux caractérisées par des biais émotionnels. Au cours de la dépression, l’émotion positive semble souvent émoussée ; dans l’anxiété, la peur et les sensations de menace peuvent être exacerbées. Il est maintenant possible d’analyser les effets des anti- dépresseurs en termes de biais cognitifs associés au traitement d’une information émotionnellement pertinente au niveau de la perception ou de la mémoire. Et les mécanismes de réentraînement ou d’exposition dans les théra- pies cognitivo-comportementales peuvent être analysés en référence aux modifications neurales sous-jacentes. Ainsi, et nous le montrerons ici, tout comme les antidiépresseurs traitent—étonnamment—la dépression, qui est un trouble émotionnel, il est possible que les traitements sérotoninergiques entraînent également un émoussement émotion- nel. Cette observation était au départ clinique mais des études en double aveugle avec des échelles appropriées montrent que des antidiépresseurs peuvent être différemment impliqués dans cet effet. S’intéresser particulièrement aux mécanismes de l’émotion en ne les considérant plus que comme de simples phénomènes, offre de nouvelles voies pour comprendre comment les émotions sont émoussées dans la dépression et dans quelle mesure c’est une caractéristique fondamentale de l’humeur dépressive et de sa rémission.

Emotional blunting in anxiety and depression – Goodwin

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The economic burden of anxiety and depression

by A. G. Wade, United Kingdom

Mood and anxiety disorders are chronic illnesses contributing substantially to the burden of illness, and unipolar depression is projected to be the second most common cause of disability worldwide by 2020. The resulting disability has an economic impact on the patient, the health care system and, mainly due to employment issues, society in general. Effective treatments are available, but at significant cost. During a time of limited resources within most health care systems, it is important that physicians are able to participate fully in any debate about budget allocation. They are only in a position to influence these decisions if they understand how economic evaluations are made. Underdiagnosis of mood and anxiety disorders is a significant problem, particularly for the following three groups of patients: those within the community who simply do not present for care; those presenting in primary care, but complaining of physical symptoms; and those with significant physical illness attending specialist clinics where the concentration of effort will be on the physical disease. More aggressive treatment with the aim of achieving remission rather than merely symptom reduction is needed. Improving compliance with treatment schedules and collaborative management are the most efficient use of current resources to attain improved outcomes for both the patient and society.

Medicographia. 2012;34:300-306 (see French abstract on page 306)

Why should physicians be concerned about economics? Faced with an individual patient, we want to do the best for that person regardless of cost. But we need to look beyond the individual patient and consider the bigger picture. We live in a time of economic constraints, with health care costs increasing faster than general inflation. For many developed countries, demographics indicate that the ratio of elderly people relative to the productive workforce is also increasing, which further compounds the problem. It is important to appreciate that demand for medical services can be almost infinite, while resources are definitely finite. The consequence is that treatment options available for an individual patient may be restricted by economic decisions determined by politicians, managers, and others. It is vitally important for the well-being of patients that doctors understand fully the financial implications of medical interventions so that they can influence financial decisions in the best interest of patients.1,3

It is also important that we understand the context within which decisions are being made. On a simplistic level, it is easy to assume that if drug A costs more than drug B...
to treat the same condition, it is sensible to use drug B. But what if drug A prevents the need for the patient to be admitted to hospital or does not require the time of a nurse to administer the treatment? Hospital costs and nurses salaries may not come out of drug budgets, but should certainly be considered when choosing drug A or drug B. Similarly, from a patient perspective, drug A may get them better quicker, may allow them to continue working during treatment, and may have fewer undesirable side effects. How may these be considered when choosing one drug over another? Even more difficult is comparing across diseases. How does one compare making someone well from acute depression and preventing a myocardial infarction by treating their hypertension for many years? This is the science of medical economics. An inexact science heavily influenced by philosophy and prejudice.

Assessing and reporting the costs of medical interventions

Unfortunately, economic evaluations of medical treatment are not simple and are heavily influenced by methodological issues and potential biases which can have an enormous influence on outcomes.

Costs related to illness

In general, there are three sources of cost related to illness. First, there are direct costs of health care. These are probably the simplest to understand, but are not without confounders, and include such items as the costs of hospital admission, diagnostic services, medical time, drugs, and overheads directly related to the health care system.

Second, there are direct nonmedical costs of health care, including provision of special social care services, such as modified accommodation for disability or social support services within the community.

Third, there are indirect costs. These may include lost production due to unemployment, reduced efficiency while at work (presenteeism), early retirement, or premature death. At a time of high unemployment in many countries, this can be a source of considerable discussion. Nevertheless, the economic impact of mental disorders on productivity should not be underestimated. While the absolute figures may now be out of date, more than half the cost of depression in the US in the 1990s was accounted for by absenteeism and presenteeism (Figure 1). As the proportion of cost attributed to inpatient care is likely to have fallen, the impact of work-related costs today is likely to be even greater. These figures are reflected in recent estimates of European costs for mood disorders, where over 60% is attributed to indirect costs. By contrast, the indirect cost of anxiety disorders is less than 40%. This suggests that the functional impact of at least some anxiety disorders might be such as to permit continued employment.

As mental disorders are particularly prevalent in the working-age population, the impact on employment and productivity is significantly greater than that of physical diseases, such as diabetes and cardiovascular disorders (Figure 2). The costs of other factors, such as medical research, crime in relation to some mental disorders such as addiction, and informal care by relatives and friends might be handled differently in different circumstances.

Reporting overall cost of illness

When reporting the overall cost or burden of an illness, there are two basic approaches. The incidence of the disease, i.e., the number of new cases in a year, can be taken and costs cal-

**Figure 1. Components of the cost of depression.**

**Figure 2. Mean number of work days lost in the past 30 days for mental and physical disorders.**

---

**Table:**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mean WLD index (per month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disorder</td>
<td>3</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>23</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12</td>
</tr>
<tr>
<td>Heart disease</td>
<td>18</td>
</tr>
</tbody>
</table>

*Updated analysis (June 2005) of the ESEMeD/MHDEA 2000 data.
The economic burden of anxiety and depression – Wade

Very often, the costs of individual illnesses are reported on a national, international, or in the case of the World Health Organization, global basis. It is important to remember, however, that economic data produced for one country or one region are not necessarily transferable elsewhere as there are wide discrepancies between the burden of illness and medical expenditure throughout the world (Figure 3).9

By the very nature of these figures, they are extremely rough estimates with “double counting” not uncommon. For example, symptoms of anxiety are frequently present within the syndrome of major depression and vice versa. It is important that the total cost of treatment is not assigned to both disorders. Figures for burden of disease assessments are produced within a political environment, often by experts enthusiastic to ensure maximal funding for research and for patients suffering from diseases in which they have a vested interest.10 This potential conflict of interest is seldom considered.

Comparing the cost burden of different illnesses
If restricted resources are to be equitably assigned, it is important that we are able to compare the value of one medical intervention with another. Is one intervention for treating depression more beneficial than another? What benefit does the patient and society get from replacing an osteoarthritic hip compared with carrying out a coronary angioplasty? In general, this is done by assessing the improvement in the patient’s quality of life and time for which that improvement is enjoyed for each intervention.

Validated scales measuring quality of life fall generally into two categories. Firstly, illness-specific scales, for which the Quality of Life in Depression Scale (QLDS)11 might be considered a good example. This has been specifically developed to assess the impact of changes in the level of depression on the quality of life experienced by the patient. Disease-specific scales tend to be more sensitive to changes in a particular illness and are good for comparing different treatments within that disease area. Generic scales on the other hand, such as Euroqol EQ5D12 and the Short Form (36) Health Survey (SF-36),13 may be less sensitive in recognizing changes in a specific disorder, but have been specifically developed in an attempt to allow comparisons between illnesses.

All illnesses are considered to reduce the quality of life of the patient and medical interventions strive to improve the quality of life. By measuring the improvement of quality of life and

Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DALY</td>
<td>disability-adjusted life-year</td>
</tr>
<tr>
<td>ESEMeD 2000</td>
<td>European Study of the Epidemiology of Mental Disorders 2000</td>
</tr>
<tr>
<td>MDD</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>QLDS</td>
<td>Quality of Life in Depression Scale</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form (36) Health Survey</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
the time for which that improvement is maintained, it is possible to obtain a figure. The most commonly used measurement is the quality-adjusted life-year, or QALY. One QALY is considered to be one year of perfect health. Depression on average reduces the patient’s quality of life by 50%, and so for each year lived with depression only 0.5 QALY is counted. Treatment of depression has the potential to gain back the lost QALY or at least part of it. The QALY gain can then be assessed against the cost of treatment, and the cost per QALY gained assessed. A patient with rheumatoid arthritis will also have a reduced quality of life for which a cost per QALY gained for treatment can be calculated. Thus, a comparison can be made between the cost of treating a patient with depression and a patient with rheumatoid arthritis. This technique is being more and more widely used by health care providers for assessing whether or not to pay for a particular medical intervention. In the UK, the National Institute for Health and Clinical Excellence (NICE)—the body charged with carrying out these assessments—has a general figure of £20-£30 000 per QALY gained as being cost effective. Despite the apparent objectivity of these measures, there is an ongoing debate at present about the value of different QALYs with, for example, gains made in increasing life expectancy at the end of life perhaps being considered more valuable than others.

A disability-adjusted life-year (DALY) is the inverse of the QALY, with 1 representing death and 0 representing a full year with no disability. An alternative to assessing quality of life is to assess “willingness to pay” for particular health gains. This is usually done at the patient level, and often displays wide discrepancies between apparent quality of life gains as assessed by QALYs and the perceived value to the patient.

The burden of anxiety and depression
When estimating the cost or burden of anxiety and depression, it is important that we consider not just patients who are treated, but also those who are untreated or inadequately treated. To do this, we need good information about the prevalence of the illness, the proportion of patients receiving treatment, the outcome of treatment, and the cost of failed treatment or nontreatment. Many community-based surveys have been carried out over the last 50 years in an attempt to assess the impact of anxiety and depression, but comparison across studies has been difficult due to the disparity in the methodology. It is hoped that the continued development of the WHO Composite International Diagnostic Interview will assist future standardization. The problem of impact assessment, however, is further complicated by the influence that depression, in particular, may have on the adverse outcome of comorbid physical disorders such as diabetes or cardiovascular disease. More recent evidence is tending, certainly for cardiovascular disease, to suggest a reduced impact of depression on clinical outcomes.

As economic assessments are often made on the basis of single disorders and often with the implicit objective of emphasizing the importance of that disorder, the possibility of “double counting” is always present. For example, insomnia may be a symptom of depression, but may also be considered a comorbid illness. It is important that we do not include the cost of insomnia as both a separate illness and as part of the cost of treating depression. This of course raises the issue of comorbidity between anxiety and depression, which has generally been ignored in economic studies.

Unipolar depression is quoted as being responsible for 8% of all disability in the US, 3.5% in the Eastern Mediterranean, and less than 1% in Africa, the different percentages probably reflecting the success or otherwise in treating other illnesses rather than a difference in the prevalence of depression itself. Unipolar depression is projected to become the second most common cause of disability worldwide by 2020, being accountable for 11.6% of the total burden of disease. It is interesting that anxiety disorders do not feature within the 10 most common causes of disability. Regardless of the accuracy or otherwise of the data, there is little doubt that depression and anxiety impose a large burden on all societies. And that burden is generally underestimated when one considers the impact on families, close relatives, and work colleagues.

The figures for anxiety tend to be reported on the basis of the individual anxiety disorders, but the most recent European figures suggest an overall prevalence of around 10%. This is similar to the figure reported in the ESEMeD 2000 study (European Study of the Epidemiology of Mental Disorders) of 8.4%, of which more than half was attributable to specific phobias.

Clinicians are aware of the presence of anxiety symptoms in virtually all depressed patients, but true comorbidity, where the symptoms of the second disorder meet the criteria for diagnosis, is particularly common in mood disorder. In the ESEMeD 2000 study, there was a particularly high association between major depressive disorder (MDD) and anxiety disorders (odds ratio [OR], 10.2; 95% confidence interval [CI], 8.2-12.7).

Managing anxiety and depression efficiently

 Recognition and diagnosis
There are three distinct groups of patients with depression for which recognition is poor: i) individuals in the community who never report to a health care professional; ii) patients presenting to general practitioners, but not necessarily complaining of symptoms of depression; and iii) patients with physical illnesses such as diabetes or cardiovascular disease, frequently being seen at specialist clinics, but where the focus is very much on the physical problem rather than the patient as a whole.

The nonreporting individuals can only be identified by screening and, in general, there is doubt about the value of this approach. Will the patients identified accept and adhere to treat-
ment? And even if they do so, will the outcomes match those of patients who seek help? Nevertheless, the US Preventive Services Task Force has recommended screening, and while this is widely acknowledged, what is often forgotten is the recommendation that it is only carried out when adequate resources are available for treatment and management. This is reiterated in the review by O’Connor: “Depression screening programs without substantial staff-assisted depression care supports are unlikely to improve depression outcomes.”

More than 90% of patients with mental health problems are treated in primary care. In the WHO study on Psychological Problems in General Health Care, in 26% of individuals visiting their general practitioner, 17% had some depression and 8.5% had generalized anxiety disorder, of whom 44% had comorbid depression. Despite the production of simple screening tools, some as simple as a single question, major efforts at educating doctors and their staff, and the production of guidelines, the problem persists. It is unlikely to be solved by any simple individual measure, but by a combination of education of health care professionals and the general public and improved clinical management processes.

The management of chronic physical illness may be adversely impacted by depression comorbidity. This being the case, it should be possible in specialist clinics to specifically screen for depression and make available the resources to manage it.

Efficient treatment

The aim of any treatment should be to achieve remission, not merely symptom improvement. The presence of residual symptomatology after an episode of depression increases the risk of relapse, a long-term chronic course, higher risks of suicide, poor social functioning, and poor outcome. The difficulty is to define remission, but from the patient’s perspective it includes the features of positive mental health such as optimism, self-confidence, the return to normal self, and good functioning. Regardless of how well the patient is following short-term treatment, it must always be borne in mind that both anxiety and depression are chronic illnesses for which long-term management should be considered. The efficacy of antidepressant medication is most clearly demonstrated in the prevention of recurrence or relapse following successful short-term treatment. For depression, each recurrence becomes more difficult to treat, and the intervals between episodes become progressively shorter.

Aggressive management based on prediction

The longer a patient persists with symptoms of depression, the more difficult it will be to achieve full recovery. It is logical, therefore, that the sooner patients are treated and the sooner they achieve remission, the better. There is a general perception that antidepressant drugs have a slow onset of effect and that with time improvements will continue to occur. In fact, evidence of improvement can be detected within a few days, and lack of clinical improvement by 14 days predicts a poor outcome.

It is reasonable clinical practice, therefore, that if improvement is not seen early in the course of treatment, consideration should be given to altering treatment. Similarly, it has been shown that if by eight weeks the patient has failed to achieve response (50% improvement in symptoms), the longer-term outlook is poor and more aggressive management should be considered.

Compliance

Akerblad demonstrated in a two-year follow-up study superior long-term recovery in patients adherent to medication. A relationship between medication adherence and reduced short-term disability in an employed population treated with antidepressants has also been demonstrated. Nevertheless, as with all chronic diseases, compliance with treatment is a significant problem in both anxiety and depression and may be particularly poor in patients with depression.

Improving outcomes

Simple interventions are unlikely to solve the problem of poor outcomes in depression and anxiety treatment, but improved compliance and improved outcomes may currently be achieved by a combination of initiatives: i) education of doctors and the general public; in general, it has not been possible to show the benefit of education programs, but without education it is difficult to imagine that progress will be made; ii) patient participation in decision-making about treatment; iii) frequent patient contact, which may not necessarily be face-to-face; and iv) improved general management of care involving all members of the medical team.

We should not underestimate the current success at treating mood and anxiety disorders; even with limited available resources much improved outcomes can be achieved by efficient clinical management.

References

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Keywords: anxiety; burden of illness; depression; disability-adjusted life-year; health care cost; quality-adjusted life-year
Les troubles de l’humeur et de l’anxiété sont des maladies chroniques qui pèsent beaucoup sur la santé et la dépression unipolaire sera la deuxième cause d’incapacité dans le monde en 2020. Cette incapacité a un impact économique sur le patient, le système de santé et, principalement en raison des questions d’emploi, sur la société en général. Des traitements efficaces sont disponibles mais à un coût significatif. Les ressources de la plupart des systèmes de santé étant limitées de nos jours, il est important que les médecins soient capables de participer pleinement aux débats ayant trait à l’attribution des budgets. Ils ne peuvent influer sur ces décisions qu’à condition de comprendre comment les évaluations économiques sont faites. Sous-diagnostiquer les troubles de l’humeur et de l’anxiété est un problème significatif surtout dans les trois groupes de patients suivants : ceux qui ne demandent pas à être soignés ; ceux qui se présentent au cabinet d’un médecin généraliste mais pour des symptômes physiques ; et ceux dont la symptomatologie physique significative les conduit au cabinet d’un spécialiste qui se concentrera sur ces symptômes. Les traitements doivent être plus agressifs afin d’obtenir une rémission plus qu’une simple réduction des symptômes. La manière actuelle la plus efficace d’améliorer les résultats pour les patients et la société est d’augmenter l’observance des traitements et la prise en charge collaborative.
Anxiety, depression, and somatic complaints: is it all psychosomatic?

by H.-U. Wittchen and F. Einsle, Germany

Anxiety, depression, and somatic complaints are strongly interrelated core concepts describing a wide range of subjective verbal expressions that may range from transient negative affect expressions to those associated with enduring prototypical clinically relevant mental disorders. Within a wider conceptualization of a biopsychosocial disease concept, referred to by the problematic umbrella term “psychosomatics,” this review selectively presents strong evidence that somatic and mental disorders overlap heavily. Therefore, both disorders share, with some variation in the diagnostic area, a wide variety of vulnerability and risk factors relevant to diagnosis, treatment, and prognosis. Although recent reconceptualizations of the diagnostic classification of mental disorders have improved research, knowledge of the complex multifactorial interplay of somatic and mental disorders still remains largely deficient, particularly with regard to identification of the involved causal mechanisms. It is necessary to understand these putative complex reciprocal relationships in order to develop improved, more effective treatment strategies in patients with comorbid mental and somatic disorders.

Medicographia. 2012;34:307-314 (see French abstract on page 314)

Traditional diagnostic classification systems like the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) separate mental disorders from somatic diseases as though there are clear boundary lines. It is generally accepted that this separation is artificial, not appropriately reflecting the apparent mind-body continuum, and even clinically unfortunate, as there might be as much of a somatic component in mental disease as there is a mental component in somatic disease. The situation is complicated by the term “psychosomatic.” This term entails different meanings and connotations ranging from disputed concepts of psychoanalysis and psychogenesis of diseases over multifactorial models of illness (known as the biopsychosocial model) to modern concepts denoting psychosomatics as a comprehensive, interdisciplinary framework. Modern definitions of psychosomatics require assessment of psychological and behavioral factors as well as a consideration of biopsychosocial factors in clinical routine. Besides this, modern psychosomatics should use evaluated and integrated psychological interventions not only in treatment, but also in prevention and rehabilitation. Depending on this conceptual focus, the term “behavioral medicine” is preferred by psychological and behavioral researchers as a term that more clearly separates their work from traditional psychodynamic conceptions (Figure 1, page 308).
Since the implementation of descriptive diagnostic classes and explicit diagnostic criteria in the Diagnostic and Statistical Manual for Mental Disorders (DSM),\(^5\) the idea that diseases are multicausal or psychosomatic in the modern sense has implicitly been adopted by highlighting the need for multiaxial classification and emphasizing the concept of comorbidity of, at least, mental disorders. In comparison with older classification systems, this more descriptive and atheoretical approach does not use the term psychosomatics, but suggests that all patients should be classified according to diagnostic classes of mental disorders (axis 1), the presence of personality disorders (axis 2), the presence of somatic diseases (axis 3), the presence of psychosocial precipitants (axis 4), and the current psychosocial functioning status (axis 5). However, it is fair to state that this stringent multiaxial classification approach has never received overwhelming acceptance both in research and practice. Furthermore, this approach has a number of drawbacks, eg, diagnosis being categorical and not dimensional. It is nevertheless notable that the DSM classification has considerably inspired concept development in research and practice; in particular, concerning a broad range of studies examining the associations between mental and somatic disease with regard to etiopathology and care.

**Coverage and scope**

Within this perspective, this paper selectively reviews evidence about the associations between defined somatic and mental disorders, focusing on the prognostic impact of mental disorders on physical health and somatic treatment. It should be mentioned that the current knowledge base does not allow more than a simple description of associations. A more detailed clarification of the dynamic interrelationships over time as well as the determination of causal mechanisms is currently not feasible. There is an extremely large number of studies...
that have examined the association of mental disorders, including anxiety, depressive and somatoform disorders, and somatic illness. This paper focuses on some common somatic illnesses, namely coronary heart disease (CHD), myocardial infarction (MI), diabetes, cancer, and other chronic “somatic” conditions (eg, asthma), as it is not possible to review all studies about the association of mental and somatic disorders. We considered including the vast array of studies about mental disorders and pain syndromes (eg, headache, back pain), but discarded this initial idea because pain is a syndrome that cannot easily be classified as being somatic or mental. We also do not deal explicitly with somatoform syndromes, because of the unclear and much disputed nosological status of these conditions and ongoing discussions of their diagnostic reconceptualization.

In primary care samples, where patients are randomly picked among primary care attenders, results appear at first glance to be different from those for community samples. For example, in the DETECT study (Diabetes cardiovascular risk Eval-

<table>
<thead>
<tr>
<th>Association of mental and somatic disorders in community and primary care</th>
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<tr>
<td>Gureje recently provided the most comprehensive and detailed epidemiologic evidence of associations between mental and somatic disorders adjusted for age and gender based on community samples in the World Mental Health Surveys (Table I). Because anxiety, mood disorders, and somatic disease are highly prevalent and thus might co-occur because of their frequency simply by chance, the associations are corrected by chance agreement using the odds ratio (OR). Overall, and controlling for chance agreement, Gureje found that there are substantial associations with anxiety or mood disorders, but not for all somatic diseases. The strongest associations between mood and anxiety disorders were found for heart disease. Additional analyses showed that the associations are consistent across different cultures and similar both in developing and developed countries.</td>
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These results are in line with previous study findings from the ZARADEMP Project (ZARAgoza-DEMentia-dePression) and the Canadian Community Health Survey, both based on samples with older adults (>55 years of age). In the study of Lobo-Escolar et al., the association between somatic diseases and mental disorders had an overall OR of 1.61 (95% confidence interval [CI], 1.38-1.88), controlled for age, gender, and education. Interestingly, the association diminished when including hypertension (OR=0.85; 95% CI, 0.71-1.02). The study by El-Gabalawy et al showed that gastrointestinal and lung disease had the highest associations with anxiety and not heart disease. Although the vast majority of community studies do not report findings for cancer, Greer et al, based on data from the US National Comorbidity Study Replication (NCS-R), showed that long-term cancer survivors suffer more often from anxiety disorder (OR=1.49; 95% CI, 1.04-2.13), especially specific phobia (OR=1.59; 95% CI, 1.06-2.44) and medical (eg, blood injury) phobia (OR=3.45; 95% CI, 1.15-10.0) than those without cancer histories.

### Table I. Age- and sex-adjusted odds ratios for mental disorders (12-month prevalence) among persons with asthma, diabetes, heart disease, and obesity.

<table>
<thead>
<tr>
<th>Mood disorder</th>
<th>Asthma</th>
<th>Diabetes</th>
<th>Heart disease</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
<td>1.6 (1.4-1.8)</td>
<td>1.4 (1.2-1.6)</td>
<td>2.1 (1.8-2.4)</td>
<td>1.1 (1.1-1.2)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>1.7 (1.4-2.1)</td>
<td>1.3 (1.0-1.7)</td>
<td>2.4 (2.0-3.0)</td>
<td>1.1 (1.0-1.2)</td>
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<tr>
<td>Anxiety disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1.7 (1.4-2.1)</td>
<td>1.6 (1.3-2.0)</td>
<td>2.1 (1.7-2.5)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Agoraphobia or panic disorder</td>
<td>1.7 (1.4-2.0)</td>
<td>1.5 (1.1-1.9)</td>
<td>2.7 (2.2-3.3)</td>
<td>1.3 (1.1-1.4)</td>
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<td>Social phobia</td>
<td>1.3 (1.1-1.5)</td>
<td>1.3 (1.0-1.6)</td>
<td>1.9 (1.5-2.5)</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>Posttraumatic stress disorder</td>
<td>1.8 (1.4-2.3)</td>
<td>1.3 (1.0-1.8)</td>
<td>2.3 (1.8-2.9)</td>
<td>1.3 (1.2-1.5)</td>
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<thead>
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<table>
<thead>
<tr>
<th>Neoplasms</th>
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<td>Cancer disease</td>
<td>194</td>
<td>11.8</td>
<td>1.7</td>
<td>1.4-2.0</td>
<td>1.5</td>
<td>1.3-1.7</td>
</tr>
</tbody>
</table>

| Endocrine, nutritional, and metabolic diseases |          |          |          |          |          |          |
| Hyperlipidemia                                | 1209     | 8.2      | 1.2      | 1.1-1.3  | 0.9      | 0.8-1.0  |

| Diabetes mellitus, type 1                     | 30       | 11.2     | 1.7      | 1.1-2.4  | 1.1      | 0.7-1.7  |

| Diabetes mellitus, type 2                     | 648      | 8.9      | 1.3      | 1.2-1.4  | 0.9      | 0.8-1.0  |

| Nephropathy                                   | 99       | 11.7     | 1.7      | 1.4-2.1  | 0.9      | 0.7-1.2  |

| Retinopathy                                   | 118      | 12.0     | 1.7      | 1.4-2.1  | 0.9      | 0.7-1.2  |

| Neuropathy                                    | 236      | 13.4     | 2.0      | 1.8-2.3  | 1.2      | 1.0-1.5  |

| Diabetic foot syndrome                        | 90       | 13.3     | 2.0      | 1.6-2.5  | 1.0      | 0.7-1.3  |

| Obesity                                       | 1381     | 8.2      | 1.2      | 1.1-1.2  | 0.9      | 0.8-0.9  |

| Thyroid disease                               | 468      | 8.3      | 1.0      | 0.9-1.1  | 0.9      | 0.8-1.0  |

| Hyperuricemia                                 | 281      | 8.2      | 1.2      | 1.1-1.4  | 0.7      | 0.6-0.8  |

| Cardiovascular disease                        |          |          |          |          |          |          |
| Hypertension                                  | 1377     | 7.6      | 1.0      | 1.0-1.1  | 0.7      | 0.6-0.8  |

| Coronary heart disease                        | 628      | 10.2     | 1.7      | 1.5-1.9  | 1.2      | 1.1-1.4  |

| Stable angina pectoris                        | 206      | 9.8      | 1.4      | 1.2-1.6  | 1.0      | 0.8-1.2  |

| Unstable angina pectoris                      | 68       | 11.8     | 1.7      | 1.3-2.2  | 1.2      | 0.9-1.6  |

| Myocardial infarction                         | 249      | 12.0     | 2.0      | 1.7-2.3  | 1.4      | 1.2-1.7  |

| Percutaneous transluminal angioplasty         | 155      | 10.6     | 1.6      | 1.4-2.0  | 1.1      | 0.9-1.4  |

| Bypass surgery                                | 133      | 12.5     | 2.0      | 1.7-2.5  | 1.5      | 1.2-1.8  |

| Left ventricular hypertrophy                  | 281      | 10.1     | 1.5      | 1.3-1.7  | 0.8      | 0.7-1.0  |

| Heart failure                                 | 442      | 11.0     | 1.7      | 1.5-1.9  | 1.2      | 1.0-1.3  |

| Atrial fibrillation                           | 152      | 9.2      | 1.3      | 1.1-1.5  | 0.9      | 0.8-1.1  |

| Peripheral arterial disease (symptomatic)     | 121      | 13.2     | 2.1      | 1.7-2.5  | 1.3      | 1.1-1.7  |

| Peripheral arterial disease (asymptomatic)    | 86       | 12.4     | 1.9      | 1.5-2.4  | 1.2      | 0.9-1.5  |

| Carotid stenoses                              | 85       | 12.0     | 1.8      | 1.4-2.2  | 1.1      | 0.8-1.4  |

| Diseases of the nervous system                |          |          |          |          |          |          |
| TIA/PRIND                                     | 137      | 14.6     | 2.2      | 1.8-2.7  | 1.6      | 1.3-2.0  |

| Cerebral insult                               | 129      | 15.9     | 2.5      | 2.1-3.1  | 1.8      | 1.5-2.3  |

| Diseases of the digestive system              |          |          |          |          |          |          |
| Gastrointestinal disease                      | 451      | 9.8      | 1.4      | 1.2-1.5  | 1.2      | 1.0-1.3  |

| Hepatic disease                               | 234      | 12.5     | 1.9      | 1.6-2.2  | 1.4      | 1.2-1.6  |

| Diseases of the musculoskeletal system         |          |          |          |          |          |          |
| Polymyalgia/rheumatism                         | 420      | 10.9     | 1.5      | 1.4-1.7  | 1.3      | 1.2-1.5  |

| Osteoporosis                                  | 243      | 9.8      | 1.2      | 1.1-1.4  | 1.0      | 0.9-1.2  |

| Diseases of the genitourinary system           |          |          |          |          |          |          |
| Bladder/renal disease                         | 220      | 10.2     | 1.4      | 1.2-1.6  | 1.1      | 0.9-1.3  |

% (w), Percentage of patients with DSQ (N=51 206) weighted for age and gender of the whole sample; OR adjusted for age and gender; reference group=patients without the respective diagnosis; other diseases are possible; Model 1=unadjusted; Model 2=adjusted for the number of somatic comorbid diseases (dimensional).

**Table II.** Prevalence and associations of depression and different somatic diseases in a primary care setting (DETECT).

**Abbreviations:** CI, confidence interval; DETECT, Diabetes cardiovascular risk Evaluation: Targets and Essential data for Commitment of Treatment; DSQ, depression screening questionnaire; N, number; OR, odds ratio; TIA/PRIND, transient ischemic attack/ prolonged reversible ischemic neurologic deficit.

such as cancer and cardiac disease. When searching for publications using the Web of Science database for the years 1990 to 2012, 13,535 results can be found for “anxiety and disease” and 37,655 for “depression and disease.”

Reviews point out that for cardiovascular disease (CVD) 15% to 20% of patients suffer from depressive disorders; among cancer patients, the median prevalence was 16.5% (95% CI, 13.1-20.3). This constitutes, in comparison with community surveys, a 2- to 3-fold increase in the risk of depression. In both domains, clinical research on comorbid depression has strongly focused on deriving clinically useful typologies, underlying mechanisms, and implications of these substantial associations. For example, a current research question in cancer patients concerns the distinction between “true” depression versus cancer-related fatigue, which might mimic depression, as well as the underlying psychosocial and neurobiological pathways involved, and respective treatment implications. Similarly, in CVD-depression research, the role of reciprocal pathways in etiology and the complication role of depression for the course of CVD and premature mortality and treatment implications have been emphasized and will be reported later in this review.

Regarding anxiety disorders, the clinical research focus has shifted from generic measures of anxiety to studying the impact of specific anxiety (e.g., panic and generalized anxiety disorder) and stress-related disorders. In recent years, for example, Spindler and Pedersen discussed the role of trauma and posttraumatic stress disorder (PTSD) in patients with cardiac diseases, and Kangas, Henry, and Bryant their role in cancer patients. Both reviews highlight the problematic definition of what constitutes a traumatic event in medical settings. Traumas in medical settings differ from others because the stressor is internally induced, and the effect of the stressor mostly lies in the future. Hence, to clarify the impact of PTSD in medical settings, more research about specific definitions of trauma in this context, as well as a differentiation from adjustment disorders, is necessary.

The impact of anxiety and depression on physical health and its treatment

There is strong evidence that a comorbid anxiety and/or depressive disorder negatively affects the severity and the outcome of somatic disease. Measured dimensionally, patients with somatic disease and comorbid mental disorders report a significantly decreased physical and mental quality of life in comparison with somatically ill persons without mental disorders, independent of type of somatic disease and mental disorder.

In addition to quality of life, another problematic topic associated with mental disorders is noncompliance, which includes nonadherence to medical treatments and no reduction in behavioral risk factors, such as smoking. For example, the DETECT study showed that, in patients with type 2 diabetes, depression at baseline predicts problematic medication compliance as well as unsatisfactory glycemic control at follow-up.

Fichter et al pointed out that comorbidity of mental disorders increases mortality risk in somatically ill patients. These results have been confirmed, especially with regard to impact of depression on mortality risk. For example, comorbid depression is associated with an at least 2-fold increased risk of mortality in patients with heart disease. Patients with diabetes and comorbid depression also have an increased risk for higher disability and mortality. Meta-analyses by Satin and Pinquart and Duberstein show that patients with cancer and major or minor depression have a 1.19 to 1.35 higher mortality risk than patients without comorbid depression. Mortality risk is increased not only by severe depressive symptoms, as even minimal subthreshold depressive symptoms have an independent effect on mortality. There is also evidence of a higher mortality risk in anxiety disorders, but results are inconsistent. As an example of a “positive” association, mortality rate was significantly higher in patients with a transplantation-related PTSD. It is possible that this finding resulted from worse compliance in these patients, or the fact that PTSD itself is predictive of poor outcome. There may be a need to consider the course of anxiety symptoms over time in order to better predict medical outcomes.

These results show the impact of mental disorders on physical health risks in particular. However, it is unclear to what degree the treatment of a mental disorder affects mental symptoms and somatic risks. Different reviews have summarized that psychological treatments in general have been shown to...

![Figure 2. Odds ratios (ORs) for depression as a function of the number of comorbid somatic diseases. OR adjusted for age and gender. Modified from reference 14: Pieper et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2008;51(4):411-421. © 2008, Springer Medizin Verlag.](image-url)
reduce depression and improve quality of life in cardiac patients. The benefit with respect to improved clinical outcomes has not been conclusively demonstrated. The literature available on treatment of anxiety in patients with somatic disease is quite restricted. Some studies report a decrease in anxiety symptoms, but likely due to the focus of treatments on depression, no improvement of somatic factors. It is a problem that in somatically ill patients, the focus is commonly on symptoms and unspecific treatments, instead of disorders and specific interventions. Still, unspecific psychological treatment might be useful in patients with somatic disease. For example, independent of other prognostic factors, mortality risk in women with CHD decreased after participation in group-based psychosocial intervention (eg, SWITCH study [Stockholm Women’s Intervention Trial for CHD]). All in all, uncertainty remains if there are subgroups of patients (eg, regarding age, gender, and social background) that benefit more from psychological treatments than others. Besides this, the question to ask appears to be what ingredients are needed for successful intervention. Whalley et al have reported 4 predictors regarding the success of interventions for depression: i) having an aim to treat type-A behaviors, ii) having an aim to educate about cardiac risk factors, iii) inclusion of client-led discussion and emotional support, and iv) inclusion of family members in the process.

Processes to explain the association of mental disorders and somatic disease
The mechanisms for the association between mental and physical disorders remain understudied. Most of the research in this area focuses on the effect of depression on chronic physical conditions, especially heart diseases. Nevertheless, two causal perspectives are conceivable.

◆ From mental disorders to somatic disease
There is more evidence that mental disorders are predictors for the development of somatic diseases than vice versa. Depression and/or anxiety predicted the development of CHD, cerebrovascular disease, and asthma in several studies. Moreover, Scott et al reported that patients with comorbid anxiety-depression disorders had stronger associations with physical disease than patients with a single mental disorder.

To explain this finding, a potential mechanism being discussed is a greater adrenocorticotropic hormone (ACTH) response in patients with comorbid anxiety-depression. For the biological pathway, “stress” is a plausible explanation: depression and anxiety go along with changes in the autonomic nervous system (including the sympathetic adrenal medullary [SAM] axis and hypothalamus-pituitary-adrenal [HPA] axis). Such dysregulations are also associated with changes in the immune, cardiovascular, and metabolic systems. Regarding somatic diseases in patients with mental disorders, the behavioral pathway is based on increased risk behavior, like smoking, binge eating, or lack of exercise. The behavioral pathway also includes the problem of reduced compliance for medical treatments (as addressed above under the section “The impact of anxiety and depression on physical health and its treatment”) as well as the modification of behavioral risk factors (eg, commencement of sports activities) in patients with mental disorders.

◆ From physical disease to mental disorder
The other direction—from somatic disease to mental disorder—is under-researched. This might be explained by the fact that most patients with somatic disease do not fulfill the criteria of a mental disorder. Nevertheless, there is evidence that persons with a somatic disease, like type 2 diabetes, have an increased risk of developing incident depression. One possible process explaining why so many stay mentally healthy after a severe somatic disease was reported by Leventhal et al, suggesting that people seek information for a better understanding of the development and course of their somatic disease and to be able to cope with the critical situation. Besides this, it may be assumed that factors associated with the development of psychological disorders in general also play a role in patients with somatic diseases. Thus, a chronic physical disorder can be seen as a stressor or critical life event and therefore play a role in vulnerability-stress models about the development of mental disease. For example, disability and constraints due to a somatic disease increase the risk of depression’s onset. Also, social consequences of chronic diseases, like loss of amplifiers, affect the risk for mental disorders. Furthermore, increased attention has recently been paid to the multitude of direct and indirect neurobiological pathways. There, physical disorders go along with endocrine, metabolic, as well as immunological changes leading to symptoms of anxiety or depression.

◆ Bidirectionality and shared risk factors
Focusing on only one direction from somatic to mental or from mental to somatic, might be too narrow. As described, depression increases the risk for CHD as well as diabetes. The somatic disorder itself goes along with disability and loss of amplifiers and can therefore intensify the depression. Hence, the concept of bidirectionality is important for understanding the association of mental and physical disorders. Similarly, it is well established that anxiety is typically a primary, and most frequently lifelong, disorder starting in childhood and adolescence, associated with increased risk of temporally secondary depression. Because of this highly complex interplay of various system components, the assumption of common shared risk factors and core etiopathogenic pathways is certainly the most promising way forward.

Corresponding studies showed that early childhood adversities produce vulnerabilities not only for mental disorders, but also somatic diseases and suggest that enduring changes in the regulation of the HPA axis is a potential common pathway. However, there are additional factors, such as socioeconomic status, whose impact on the association between mental and somatic disease is under discussion.
Conclusion
Anxiety, depression, and somatic complaints are strongly interrelated core concepts describing a wide range of subjective verbal expressions that may range from transient negative affect expressions to those arising from enduring prototypically clinical relevant mental disorders. Within a wider conceptualization of a biopsychosocial disease concept, referred to by the problematic umbrella term “psychosomatics”, this review selectively presents strong evidence that somatic and mental disorders overlap heavily. Therefore, both disorders share a wide variety of vulnerability and risk factors relevant for diagnosis, treatment and prognosis, with some variation in the diagnostic area. Although recent reconceptualizations of the diagnostic classification of mental disorders have improved research, the complex multifactorial interplay of somatic and mental disorders still remains largely undefined, particularly with regard to elucidation of the causal mechanisms. It is necessary to understand these putative complex reciprocal relationships in order to develop improved and more effective treatment strategies in patients with comorbid mental and somatic disorders.

References
**Dépresse, anxiété et symptômes somatiques. Tout est-il psychosomatique ?**

L’anxiété, la dépression et les symptômes somatiques sont des concepts fondamentaux fortement intriqués qui correspondent à un large éventail d’expressions verbales subjectives qui vont de l’affect négatif transitoire à l’archétype du trouble mental durable cliniquement pertinent. Se basant sur une conceptualisation plus large de la maladie biopsychosociale (représentée par le terme parapluie de « psychosomatique »), cet article, présenté de manière sélective des preuves fortes d’un recouplement important des troubles mentaux et somatiques. Ces deux catégories de troubles partagent donc, avec quelques variations dans le diagnostic, une grande variété de facteurs de risque et de vulnérabilité ayant trait au diagnostic, au traitement et au pronostic. Les réflexions récentes de la classification diagnostique des troubles mentaux ont amélioré la recherche mais la connaissance de l’interface complexe multifactorielle des troubles mentaux et somatiques reste encore très incomplète surtout en ce qui concerne l’identification des mécanismes causaux impliqués. Il est nécessaire de comprendre ces prèmes relations réciproques complexes afin de développer de meilleures stratégies thérapeutiques plus efficaces chez des patients souffrant de comorbidités mentales et somatiques.
**THE QUESTION**

Does depression exist without anxiety? These two diseases are known to be highly comorbid, but how does this manifest in real life? Twelve specialists from all parts of the world explore the pros and cons of how close this relationship between anxiety and depression really is, on the basis of their own country-specific experience of the biological, epidemiological, and clinical characteristics of anxiety and depression in their daily practice.

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Does depression exist without anxiety?

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Depressive and anxiety disorders are common in primary health care settings. Prevalence of lifetime major depression and anxiety disorders in the National Comorbidity Survey\(^1\) was 17.1% and 24.9%, respectively, with a 12-month prevalence of 10.3% for depression and 17.2% for any anxiety disorder. The survey also found that 51.2% of people with major depression also had a comorbid anxiety disorder. Furthermore, there was a high likelihood of people with anxiety disorders developing major depression.\(^1\) Several other studies have found that any anxiety disorder increased the likelihood of depression by more than two times.\(^2\) The conclusion from these surveys is that in the community and primary care settings, anxiety with comorbid depression is so common that it is the rule rather than the exception, and in the community, encountering depression without anxiety is rare. Thus it should be routine clinical practice to screen for depressive symptoms in people with anxiety disorders and vice versa.\(^2\)

Comorbid anxiety disorders in major depression are a cause of concern, as affected patients are usually more severely ill: with increasing severity of illness comes an increased tendency to chronicity, with poorer occupational and psychosocial function and a poorer quality of life.\(^3\) In the large trial NESDA (Netherlands Epidemiological Study of Depression and Anxiety), the most chronic course was identified in people with comorbid depression and anxiety disorders (57%) compared with pure anxiety disorders (42%) and pure depression (25%).\(^2\)

Comorbid depression and anxiety may present in any of four ways: depression symptoms in people with an anxiety disorder; major depression with anxiety symptoms; co-occurring major depression and anxiety disorders, and subsyndromal depression and anxiety.\(^3\) Much interest has been generated by the introduction of a diagnosis of mixed anxiety-depressive disorder and its inclusion in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). It should be noted that the aforementioned epidemiological studies reported rates of comorbid anxiety disorders in major depression rather than subsyndromal features.\(^3\)

The presence of any anxiety disorder then is an important risk factor for the development of major depression. Hence, it has been postulated that exposure to a life event leading to clinical anxiety may lead to major depression in vulnerable patients.\(^4\) There is also the added complication of general medical comorbidity. In one primary care study, patients with depression or anxiety disorders had two to three chronic medical illnesses, and people with medical illnesses had a high rate of depression and anxiety disorders.\(^4\)

Suicide risk in patients with comorbid depression and anxiety is also a cause for concern. Although about 70% of suicides are related to depression, the presence of anxiety disorders accentuates that risk. Major depression without anxiety was associated with a 7.9% suicide risk, but when comorbid anxiety was present, the risk increased to 19.8%.\(^5\)

In major depression with anxious symptoms, selective serotonin reuptake inhibitors (SSRIs) are well established as first-line medication. SSRIs are also equally effective in the treatment of anxiety disorders. However, there is little evidence of their efficacy in comorbid depression and anxiety disorders. One study on comorbid depression and panic disorder could not establish efficacy either way.\(^6\) Hence, more clinical trials are needed in comorbid depression and anxiety disorders to determine dosage, time to response, and duration of treatment, particularly in primary care.

From the perspective of the primary care doctor, major depression with comorbid anxiety should be seen as the norm. A thorough evaluation of the presence of both, assessment of suicide risk, and acknowledgment of coexisting medical illnesses should lead to an effective collaborative model. Treating the underlying conditions, understanding the long-term impact of comorbidity, educating the patient and family, and helping the patient to achieve good quality of life must be joint goals for both doctor and patient.

**References**

In clinical psychiatry, it has been repeatedly reported that depressed patients often also meet the criteria for anxiety disorders and patients with anxiety disorders often meet the criteria for depression. Several epidemiological studies have found that depression and anxiety are highly comorbid entities. Successful treatment of major depressive disorder is often associated with improvement in anxiety symptoms and vice versa. In modern pharmacotherapy, there are practically no significant differences between treatment of anxiety disorders and depression. But an open question remains: are depression and anxiety two manifestations of one disease, or are the two disorders based on two different etiologies?

As psychological concepts, depression and anxiety are mental disorders with different symptoms at the emotional, motivational, and cognitive levels. At the symptom level, the diagnostic tools DSM-IV (fourth revision of the Diagnostic and Statistical Manual of Mental Disorders) and ICD-10 (tenth revision of the International Statistical Classification of Diseases and Related Health Problems) also consider depression and anxiety to be different entities. Newer studies argue against the view that the two disorders are merely different manifestations of a single syndrome. The existence of differences in risk factors prevents us from seeing an anxiety disorder as merely a prodromal, residual, or severity marker of depression.

Challenging the notion that anxiety usually precedes depression and eventually develops into depression, recent studies show that the reverse pattern occurs almost as often. These findings seem consistent with the idea that an anxiety disorder can be viewed as a consequential disorder in itself, independent from depression.

Regardless of whether depression and anxiety are symptoms of one disease or separate entities, their comorbidity is affecting more and more of the adult population and constitutes a greater health burden than previously thought. All contemporary authors agree that >50% of adults visiting their physician during an episode of anxiety or depressive disorder will be suffering from their comorbidity. Considering their high prevalence, frequent onset in early adulthood or even childhood, mutual relationship with many somatic disorders, and negative effects on quality of life, anxiety and depression are very important worldwide health problems. The presence of depressive/anxiety comorbidity substantially increases medical utilization and is associated with greater chronicity, slower recovery, increased recurrence rates, and greater psychosocial disability. How often—and whether—the two disorders occur together is, of course, different for each patient. Despite the standardization of diagnosis and therapy and differences in theoretical opinions, we should never neglect the subjective experience of the patients who put their trust in us and should provide them with the right personalized treatment and solution.

Enormous advances have been made over the past decades in the treatment of anxiety disorders and depression. Exciting new tailored therapies that target specific neurotransmitters have been made possible by our expanding knowledge of the human brain. In this era of personalized medicine, tailoring treatment to the specific needs, values, and preferences of each patient and their family is crucial. The patient is presumed to take an active role in every part of the treatment process in collaborative partnership with the physician. It is important to enhance the patient’s personal understanding of their illness, and to promote autonomy, responsibility, and dignity. Effective clinical communication is one of the most important means of accomplishing this, using skills such as empathy and compassion. It has been recognized that the quality of the physician’s communication skills influences the overall therapeutic outcome in many ways and bridges the gap between evidence-based medicine and the individual patient. The whole person and his or her physical, mental, social, and spiritual health is the natural focus of psychiatric practice and consequently the treatment of anxiety and depression.
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Since the separation of anxiety and depressive disorders by the Newcastle School in the 1960s, large studies in community and primary care settings have continuously reported that comorbidity between the two entities is not the exception, but the rule. One recent example is a Dutch cohort study showing that 67% of patients with a depressive disorder had a current comorbid anxiety disorder (75% had a lifetime anxiety disorder); similarly, 63% of those with a current anxiety disorder had a current depressive disorder (81% had a lifetime depressive disorder). The reduced volume of the rostral-dorsal anterior cingulate gyrus, generically associated with depression and anxiety disorders in this cohort, supports a shared etiology. By contrast, the specific involvement of the inferior frontal cortex in depressive disorders and lateral temporal cortex in patients with anxiety disorders without comorbid depressive disorder probably reflects the existence of disorder-specific symptom clusters.

Comorbid major depressive disorder (MDD) and generalized anxiety disorder (GAD) have been particularly studied. The National Comorbidity Survey showed that this comorbidity does not arise from separate unitary phenomena, but from a heterogeneous collection of clinically meaningful classes. These classes include somatic and psychological symptoms of depression and anxiety covering four symptomatic domains and seven latent classes, as well as clinically meaningful subthreshold comorbid conditions.

The comorbidity of both threshold and subthreshold diagnostic levels of MDD and GAD has been demonstrated in many settings, and is always associated with symptom severity, disability, and treatment difficulties. This suggests the importance of a more dimensional approach to classification of these conditions.

Presumably, the forthcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) will include dimensions between MDD and GAD, and given the coincidence of validating factors in both categories, a negative-affect disorder including GAD and MDD may be proposed.

The comorbidity between MDD and GAD is associated with treatment barriers and worse psychiatric outcomes worldwide, including treatment resistance, increased suicide risk, greater chance of recurrence, and greater utilization of medical resources (mainly primary care). Increased recognition of the high prevalence and negative impact of comorbid depression and anxiety will lead to more effective treatment. A wide range of instruments is available for ongoing assessment of clinical status and outcome in patients with depressive or anxiety disorders. However, few doctors use these instruments in managing their patients. While it is hoped that early and effective intervention will yield long-term benefits, more research is needed to confirm this.

Unfortunately, there is no “silver-bullet” approach to the treatment of anxiety-depression comorbidity. One problem with clinical guidelines for depression and anxiety is that they do not capture the entire range of comorbid patients. Moreover, patients with comorbid psychiatric or medical conditions are usually excluded from phase 3 clinical trials, and as a consequence, scientific therapeutic information on these patients is lacking. Thus, participants in phase 3 clinical trials are not “real” patients, and there is a long and sometimes tortuous path from efficacy shown in clinical trials (determined on the basis of a single DSM-IV anxiety or depression category) to effectiveness in comorbid patients in clinical practice. Future treatment guidelines will probably improve identification of “real” patient groups and the nature of patients who may respond to particular interventions. In any case, those guidelines for the treatment of anxiety and depressive disorders must consider the clinical heterogeneity and comorbidity of anxiety and depression in patients in diverse clinical settings.

In the future, the old categories of anxiety and depression that began their journey with the Newcastle School will probably coexist with new formulations that better represent the affective dysregulation characterizing the comorbidity between anxiety and depression in a range of clinical populations.

References
Depression and anxiety are both highly prevalent diseases. The true relationship between the conditions is often unclear and has been the subject of much discussion. One of the core questions is whether anxiety and depression are separate or distinct entities with different symptoms, genetic expression, neurobiology, and associated treatment options. Given the high comorbidity of the diseases, many explanations have been put forward to explain their close relationship. These include: (i) the overlap between diagnostic criteria; (ii) one disorder being the epiphenomenon of the other; (iii) different phases of a distinct disorder; (iv) one disorder being a risk factor for the other; (v) overlap of genetic and etiological mechanisms between the two diseases; and (vi) reciprocal causation.1

The “tripartite model” proposed by Clark and Watson2 to assess distinct and shared features of mood and anxiety disorders considered that the negative affect dimension would cover general symptoms of psychological distress, common to both conditions. In fact, there are several key symptoms that overlap between depressive disorders and anxiety: sleep disturbance, poor concentration, and fatigue (especially for generalized anxiety disorder), and also irritability, decreased concentration, foreshortened future, helplessness, and loss of interest (especially for posttraumatic stress disorder).

Recent neuroimaging studies have consistently shown that both disorders show common brain abnormalities in the orbitofrontal cortex, amygdala, and hippocampus, among others. It has therefore been suggested that these disorders are both variants of the same underlying brain pathology. However, functional neuroimaging studies have observed distinct laterality and activation profiles in the amygdala for depression and anxiety disorders. There are also genetic commonalities between both disorders that are supported by family and twin studies and genetic data, such as the methylation level of the serotonin transporter (5-HTT), which is in part influenced by environmental factors.3 Moreover, the current first-line treatments for depression and anxiety include selective serotonin reuptake inhibitors, selective serotonin norepinephrine reuptake inhibitors, and other atypical antidepressants, as well as cognitive behavior therapy or combination therapy.

Although mood and anxiety disorders share many symptoms, they are conceptualized as being diagnostically distinct disorders by the classification systems currently in use. Some authors, however, have proposed a dimensional approach to the classification of depression and anxiety along a continuum of symptom severity, degree of suffering, and impairment, rather than arbitrarily defined categories. This could be a more valid approach. The use of a dimensional approach provides continua along the different depression and anxiety domains, and an individual clinical state can be determined by the pattern of a specific dimensional score, thus covering the full spectrum of severity, from healthy to pathological.4 Although these constructs can distinguish one condition from another, it is well established that anxiety symptoms are typically moderately-to-highly correlated with depressive disorders, as are depressive symptoms with most anxiety disorders. The same overlap is true of subsyndromal anxiety and symptoms of depression without the full-blown diagnosis, as well for the mixed anxiety-depressive disorder. Consequently, even a dimensional view of the correlation between depression and anxiety lacks the more objective criteria necessary to discriminate between these conditions.

In conclusion, concurrent symptoms of depression and anxiety may either represent distinct disorders with overlapping symptoms, or different manifestations of a shared underlying neurobiological vulnerability.5 Future studies using external validation, including pharmacological and behavioral challenges investigating biological mechanisms, functional neuroimaging studies, and cognitive-behavioral approaches, are thus desirable and necessary in order to enable clarification of this issue.

References
Why are clinicians interested in the comorbidity between depression and anxiety? A key reason is that patients with comorbid anxiety and depression are often more resistant to pharmacological treatment and have a poorer medical prognosis than with either disorder alone.

The lifetime prevalence of major depressive disorder (MDD) and anxiety disorders is 17% and 25%, respectively. The majority of patients with an anxiety or depressive disorder present with, or develop, other comorbid psychiatric conditions. In the US National Comorbidity Survey, 58% of patients with MDD had a comorbid anxiety disorder and 67% of patients with generalized anxiety disorder (GAD) had a lifetime history of comorbid unipolar depressive disorder. Among subjects with panic disorder without agoraphobia, 47.2% had obsessive compulsive disorder, and 40.7% had a lifetime diagnosis of major depression. The lifetime prevalence of specific anxiety disorders among subjects with a lifetime diagnosis of MDD is significantly higher than the prevalence of these anxiety disorders in the general population. The largest clinical sample of patients with MDD in which the phenotype of anxious depression has been studied comes from STAR*D (Sequenced Treatment Alternatives to Relieve Depression): a total of 53.2% met the criteria for anxious depression in Level I treatment (21% of patients with comorbid MDD and syndromal anxiety, 79% with MDD and subsyndromal anxiety). In nonclinical samples from Europe among people aged 18-65 years, approximately 30%-40% of patients with depressive disorder had a comorbid anxiety disorder, and vice versa. In later life studies among people aged 55-85 years, 47.5% of those with MDD also met the criteria for at least one anxiety disorder, and 26.1% of those with anxiety disorders had MDD.

Comorbid depressive and anxiety disorders may represent discrete disorders or different manifestations of a shared underlying neurobiological vulnerability. There is a biological relationship between anxiety and depression, including a shared genetic diathesis, and at least some genotypic association has been defined in a comorbid study group. Twin studies suggest a remarkable degree of overlap in genetic risk for GAD and MDD, but the environmental determinants are different. Anxiety disorders with an earlier age of onset may be a stressor triggering an underlying neurobiological vulnerability to depression, perhaps through serotonergic dysregulation or induction of hypothalamic-pituitary-adrenal axis dysfunction. The findings of brain imaging studies suggesting the additive effects of anxiety and depressive disorders is not sufficient to explain the patterns associated with depression and anxiety.

How well is the comorbidity of depression and anxiety disorders recognized and treated? Although awareness of anxiety and depressive disorders is increasing among the general population, anxiety and depressive disorders are frequently underrecognized, underdiagnosed, and undertreated. Epidemiological studies have demonstrated that depressed individuals with a history of anxiety disorders are at increased risk for hospitalization, suicide attempt, and greater impairment from the depression. As mentioned, comorbid anxiety and depression is often more resistant to pharmacological treatment and is associated with a poorer medical prognosis than either disorder alone. No treatment has been clearly shown to be more efficacious in patients with comorbid depression and anxiety.

With the information given here, it is clear that depression cannot exist without anxiety because of the high comorbidity rates among clinical and nonclinical samples and also the common shared neurobiological vulnerability. The presence of comorbid anxiety and depression is associated with a greater severity of symptoms, greater impairment, and poor response to pharmacological treatment. It is therefore very important in clinical practice to recognize comorbid anxiety disorder in psychiatric outpatients with a principal diagnosis of MDD, and to consider treatment with an antidepressant that has a broader indication that also covers anxiety disorder.

References
Although comorbidity between depressive and anxiety disorders is high, and symptoms of anxiety are often present within the structure of depression, some forms of nonpsychotic depression are without distinct signs of anxiety, as is well known by every psychiatrist.

Vital depression presents with melancholia and unreasonable pessimism, despondency, depressed mood, feelings of guilt, low self-esteem with ideas of self-purposelessness, incapacity regarding professional activity and family life, and ideomotor retardation. Its maximum impact on the patient is during morning hours. Some activity during daytime hours is maintained, and the majority of patients continue working and their everyday duties, although with difficulty. Suicidal ideations and attempts are rare.

The clinical presentation of apathic depression is dominated by a deficit of drives, with a decrease in vital tonus. All types of behavior lose their sense and are carried out as a result of necessity; “habitually,” “automatically.” Apathic affect has no expressiveness and is accompanied by a reduction in facial expression, monotonous speech, and motor retardation—which at times reaches akinetic levels. Depression manifests itself with a sudden sense of estrangement from all previous wishes, indifference to the environment and self-position, and an absence of interest in the results of one’s activity and previous involvement in life events. These changed sensations differ greatly from premorbid sensations. Dismal depression with a conscious awareness of the changes in one’s affective life comes to the foreground.

Apathic depression (depression of exhaustion) includes increased levels of exhaustion, activity reduction, tearfulness, complaints of physical weakness, and loss of energy; “dilapidation.” Each activity is associated with a need to overcome weakness, and brings no satisfaction. A sense of fatigue appears even with insignificant effort. Changes in self-sentiment often have a circadian rhythm characteristic of depression, which is expressed as oppression, fatigue, and distressing self-sentiments in the morning hours (just after night sleep). Depressive asthenia differs by way of a resistance to and absence of connection with activities. In more clinically apparent depression, complaints include difficulties in performing routine morning procedures (washing, dressing, combing one’s hair), which are exhausting and need considerably more time than normal. Also in evidence are signs of irritable weakness and asthenic hyperesthesia, with excessive sensitivity to sensory stimuli and an intolerance of external irritants (loud sounds, bright light, etc). Affective symptoms alone are limited: melancholy, anxiety, ideas of low self-value, and feelings of guilt are not typical.

Presentation of anesthetic (depersonalization) depression consists of emotional alienation and its diffusion into interpersonal relationships (loss of emotional resonance) and the environment. Depressive alienation may acquire a generalized character, with painful insensibility (anesthesia psychica dolorosa) and a distressing awareness of the loss of emotions (no mood, no desires, no boredom, no anguish, and no feelings for close relatives or even one’s own children). Events that occur in the environment do not find any response in the soul; everything seems to be changed, unnatural, foreign, and distant. Alienation phenomena are often accompanied by loss of a sense of delight and the ability to be glad and to experience pleasure. Depression with alienation involving the somatosensory drives is limited to somatic manifestations (somatic equivalents of depression): a sudden loss in the need for sleep, low food intake (depressive anorexia), and decreased libido until there is a total loss of sexual desire. Food aversion is accompanied by a refusal to take in food and insufficient nutrition, with significant weight loss in the first 1–2 weeks of the illness.

Thus, anxiety symptoms reveal themselves predominantly during depression with hyperesthesia (anxiety, self-torment, hypochondria), and as a rule are absent in vital depression and depression with alienation phenomena involving ideatoric, vital, and somatopsychic components.
Major depressive disorder (MDD) is one of several well-known chronic, recurrent, and disabling mental diseases with high direct and indirect costs to society and the family in both Western and Eastern cultures. In China, the prevalence of anxiety disorders ranks them in third place among all mental illnesses. A report from our OPERATION trial suggested that 70% of patients with treatment-resistant major depressive disorder had anxious features. Thus the question of whether depressive disorder must exist with anxiety symptoms or anxiety disorders is now raised.

What have we learned from the diagnostic systems?

In the ICD-10 (International Statistical Classification of Diseases and Related Health Problems–10) Classification of Mental and Behavioural Disorders (World Health Organization, 1992), a patient who is diagnosed as having a “depressive episode” usually suffers from depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity. Marked tiredness after only slight effort is common. Other common symptoms are: (i) reduced concentration and attention; (ii) reduced self-esteem and self-confidence; (iii) ideas of guilt and unworthiness (even in a mild episode); (iv) bleak and pessimistic views of the future; (v) ideas or acts of self-harm or suicide; (vi) disturbed sleep; and (vii) diminished appetite.

Meanwhile, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) defines a “major depressive episode” as involving five or more of the following symptoms, at least one of which must be depressed mood or loss of interest or pleasure: (i) depressed mood; (ii) loss of interest or pleasure; (iii) significant weight loss when not dieting or weight gain; (iv) insomnia or hypersomnia; (v) psychomotor agitation or retardation; (vi) fatigue or loss of energy; (vii) feelings of worthlessness or excessive or inappropriate guilt; (viii) diminished ability to think or concentrate, or indecisiveness; and (ix) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

When looking at these different criteria, we find that both diagnostic systems are focused mainly on the patient’s depressed mood and related symptoms, with little mention of anxious symptoms.

What we have found in clinical practice

If one carefully examines patients with MDD in clinical practice, one can find that they exhibit different features during a depressive episode. For the most part, each patient does have depressed mood, loss of interest/enjoyment or lack of energy, and a series of symptoms related to depressed mood. Physical discomfort and somatic symptoms are also common, especially in Asian populations. Many patients complain of fatigue, pain, and various symptoms involving the gastrointestinal or cardiovascular systems, among others. Meanwhile, over half of MDD patients have anxious symptoms such as worry, fear, sleep disorders, and restlessness.

What we think based on the treatment medications

Currently, there are a number of types of antidepressant that are routinely and effectively used for patients with MDD, anxiety disorder, and mixed depressive-anxious disorder, including selective serotonin reuptake inhibitors, serotoninnorepinephrine reuptake inhibitors, and others. This fact implies that all of these disorders may share similar pathophysiological mechanisms. When considering that the same medications are used in depressive and anxiety disorders with similar efficacy and outcomes in both, we could conclude that comorbid anxiety disorder is not only common, but that it is an inevitable phenomenon in the psychopathology of MDD.

In summary, although the criteria for a “depressive episode” do not emphasize the importance of anxious symptoms and/or anxiety disorders, both psychopathology and psychopharmacology support the idea that “depression does exist with anxiety!”

References

The shortest answer is that depression could exist without anxiety for a certain time period, but solitary manifestation of an affective syndrome is mostly short and temporal, and it is thus only a question of time as to when the typical clinical pattern, single or multiple comorbidity with anxiety disorders, will dominate the clinical picture. Some clinicians argue that depressive and anxiety disorders are overlapping, almost indistinguishable, sharing similar genetic and pathophysiological liabilities. However, the comorbidity issue is asymmetrical, since in general, anxiety disorders have a stronger tendency to co-occur with depression than do depressive disorders with anxiety disorders.

Epidemiological research indicates that comorbidity is the norm rather than the exception. The average odds ratio is 6.6 for pairwise associations between affective and anxiety syndromes, and this is the reason that the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) introduced the concept of the mixed anxiety and depression disorder in 1992, unfortunately with high diagnostic instability. The lifetime comorbidity pattern is strong and only slightly different, depending on the marked heterogeneity of endophenotypes.

It is also only a question of time as to which comes first—whether anxiety precedes or follows the onset of an affective disorder. In two-thirds of cases, anxiety syndromes are “starters,” preceding the onset of affective syndromes, perhaps indicating a causal relationship. Shared risk factors such as common genes and pre- and postnatal environmental and biological effects reflect temporal, predictive, and causal priority for the anxiety syndrome. Nuclear family and twin studies provide an overwhelming body of evidence for the shared heritability of anxiety and depressive behavioral traits, in the range of 30%-50%.

The question of the time issue again: both depressive and anxiety disorders start relatively early in life. Genetic, biological, and social factors and stressors render the hypothalamic-pituitary-adrenal (HPA) axis hypersensitive to later challenges in both syndromes. Robust evidence exists for HPA dysregulation during the time course of certain anxiety and depressive syndromes as an indicator of disturbed (mainly increased) noradrenergic output from the locus coeruleus, leading to shared and unique anxiety sensitivity, attributional style, and autonomic arousal endophenotypes.

It is only a question of time as to when we will understand more about the development of shared and unique clinical symptoms. Depression and anxiety disorders have a number of common components such as fatigue, agitation, sleep disturbances, and concentration difficulties, and these form the basis of the conceptual similarities between existing theories of comorbidity. According to the integrative, hierarchical tripartite model of depression and anxiety, both are considered to fall into a subset of aversive psychological states with high anxiety sensitivity and metacognition, negative affectivity, low positive emotionality (in depression), and autonomic arousal (mainly in anxiety disorders).

The question of the time factor again: ample evidence indicates that the duration of comorbid depressive and anxiety syndromes affects the outcome. With greater overlap of depressive and anxiety syndromes comes a more severe clinical syndrome, higher comorbidity with other psychiatric and somatic conditions, higher risk for suicide, and shorter life expectancy.

Should we artificially differentiate mood and anxiety disorders even when we know about the substantial overlap of their clinical symptoms, epidemiology, and pathophysiology? Hopefully, it is also only a question of time as to when we recognize that the separatist approach is meaningless and we accept the idea that one should not even consider studying, diagnosing, or treating anxiety and depression separately, but rather in combination. Of course, it is only a question of time as to when we will be able to resolve these conceptual, diagnostic, pathophysiological, and treatment challenges.

References
A combination of depression with anxiety symptoms in depressive patients is more common than not. The problem lies in the diagnostic qualification of this condition—is it a comorbid existence of two independent disorders, or are the anxiety symptoms an integral part of depression? The topicality of this question is determined by our need to estimate a prognosis for the condition of depressive patients (both clinical and functional) and to choose the therapeutic intervention (its duration and intensity).

From a practical viewpoint, the anxiety symptoms—including physical and autonomic ones—have no nosological significance because they also form part of the depressive syndrome. This set of symptoms, common to anxiety and depression, comprises reduced energy levels, disturbed sleep, change in appetite, nonspecific cardiovascular and gastrointestinal complaints, difficulties in concentration, nervousness, and increased fatigability. Detection of these symptoms during different phases of the depressive episode is of paramount prognostic value.

On the one hand, we may speak about these symptoms during the prodrome and early stages of depression. During these stages of the episode, the early emergence and domination of autonomic signs over mood and psychological symptoms determines the severity of further depression dynamics (in particular, future treatment resistance and levels of functional impairment). Thus, the early existence of anxiety symptoms in the structure of the depressive episode stipulates selection of aggressive therapeutic interventions. On the other hand, we may speak about the role of anxiety during the “late” stages of a depressive episode. A usual process of remission formation is accompanied by prolonged existence of a subthreshold set of symptoms. This set is made up of the same physical and autonomic spectrum of symptoms as anxiety: sleep disturbance, concentration difficulties, obsession, tiredness, and irritability. The quantity and severity of these typical anxiety signs is not sufficient for a separate diagnosis. Therefore, we usually speak about partial remission, pointing out these subsyndromal signs. The truth is that “subsyndromal” does not mean “subclinical”. This subsyndrome anxiety involved in partial remission means the continuation of significant functional impairment.

In turn, this means a continuation of the depressive episode itself, despite our view that the level of anxiety symptoms is “subthreshold.” Furthermore, it should be kept in mind that the ongoing presence of these symptoms increases the risk of recurrence of the depression. Consequently, to reach the goal of functional recovery and to prevent subsequent episodes of depression, it is necessary to cut off residual anxiety. Thus, antidepressant treatment that has been administered should be continued.

In real clinical practice, we often see quite the opposite. Antidepressants are discontinued because of the reduction in negative mood and psychological symptoms. After a while, the existence of signs of anxiety is regarded as indicative of an independent comorbid condition (eg, insomnia or anxiety disorder) by both the patient and clinician. For this reason, the patient is prescribed hypnotics or tranquilizers. It is evident that the outcome of such treatment in a depressive patient is rather doubtful. So for some practitioners, the concept of comorbid anxiety disorders and depression forms the basis of an erroneous treatment approach to prolonged and recurrent depression.

Ultimately, we have to conclude that from the perspective of everyday clinical practice, anxiety is an integral and essential part of depression. Moreover, anxiety symptoms should be considered a significant predictor of depression severity and the level of a patient’s functional recovery, and can be utilized in choosing a treatment intervention.
H istorically, Hippocrates first spoke of melancholia, not anxiety, perhaps because at the time fear was not construed as a potential disorder. The concept of anxiety followed centuries later. Modern data consistently indicate that anxiety and depression are closely related clinical entities. Research on stress and life events has linked the two disorders even at the level of a genetic diathesis. Hormonal factors accompany psychosocial factors to produce a consistently higher incidence of both conditions in females. Common antidepressant treatment (e.g., selective serotonin reuptake inhibitors) is applicable to both conditions.

When one evaluates a patient with depression, anxiety is often found as an accompanying symptom or as a syndrome involving a mix of mental and physiological symptoms. Up to three quarters of depressed patients have been reported to manifest signs of an anxiety disorder during the course of their illness, and anxiety disorders are often comorbid with depression. Over 40% of patients with major depression have a lifetime comorbid anxiety disorder (usually phobias, social anxiety, generalized anxiety disorder [GAD], or panic disorder); this may increase suicidality.

Forms of depression such as “vital depression” are sometimes diagnosed in patients who present as depleted, lifeless, and altogether emotionless, often with somatic symptoms, but not overt anxiety. Indeed, many medically unexplained somatic symptoms are often attributed to “masked” depression, a kind of depression sine depressione.

Could such a syndrome exist for anxiety, a “masked anxiety syndrome”? It is hard to conclude accurately about a patient’s inner experience, which may very well in some cases be so agonizing that it freezes up the patient so that the usual feeling of anxiety is not recognizable. In such instances, we sometimes speak of dissociation. Anxiety is such a ubiquitous feeling across the whole normal to pathological span that one would have difficulty imagining any state of human malaise or dysphoria without an anxious component.

When we evaluate patients with anxiety, we are also likely to come across depressive features. Major depression is indeed more prevalent in patients with an active anxiety disorder. Interestingly, when both depression and anxiety are manifest, anxiety usually precedes depression rather than the reverse (57% vs 13%), and the presence of anxiety (especially multiple anxiety disorders) is more predictive of subsequent development of depression. In this respect, social phobia and GAD seem to carry the highest risk. What is the meaning of this temporal phenomenon? Could it mean that anxiety disorders act as chronic stressors to precipitate depression at some point along the way? Stressors are usually negative life events, but they can also be negative emotions, especially if they are chronic and debilitating. We are not used to thinking of mental illness as a stressor itself, but clinical experience shows that few things can be more burdening for a patient and family than mental illness, major or minor.

One recent study argues for a possible adaptive component in anxiety symptoms. In a large population survey (n=61 349) linked to a comprehensive mortality database, researchers found that case-level depression was associated with increased mortality comparable with that of smoking. Interestingly, the association between anxiety symptom load and mortality was U-shaped; those with the lowest anxiety had the highest mortality. Anxiety may mobilize depressed patients and their physicians to deal more actively with the patients’ problems.

Anxiety and depression are both very common conditions, and as such, would have a high probability of co-occurring. It is interesting to closely observe cases in which they do not co-occur. In this respect, anxiety and depression probably need to continue to be construed as separate entities so that their association can be better studied and understood.

References
If in every patient who presented with depression it were also possible to diagnose an anxiety disorder, and in every patient who presented with an anxiety disorder it were also possible to diagnose depression, probably a much longer period of time would have been needed in the history of psychiatry to recognize and conceptualize the two entities as being diverse, and the title of this article would be pointless.

Depression and anxiety disorders are more common in women than in men. The results of epidemiological studies differ according to the composition and structure of the sample populations studied and the methodologies applied. Lifetime prevalence of depression is approximately 20%-40% in women and 10%-20% in men. In one survey, anxiety was found to begin before or concurrently with depression in 37% of depression cases, and depression began before or concurrently with anxiety in 32% of anxiety cases. Cumulatively, 72% of lifetime anxiety cases had a history of depression, and 48% of lifetime depression cases had experienced anxiety.  

A high comorbidity between the two entities is apparent in all studies, but the relationship is a very complex and puzzling one. In anxiety disorders, it is possible to define different subtypes relatively clearly, while in depression, however, subtypes are blurred, the main markers of major depression being anhedonia and melancholia. A number of factors complicate the issue—the categorical versus dimensional approach to diagnosis applied in different studies, the sharing of some clinical symptoms between the two entities, certain common etiological risk factors, and a relative lack of stability of diagnosis over time (in longitudinal studies). A diagnosis of mixed anxiety-depression is already recognized in the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), and will probably be included in the future fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Depression and anxiety have been viewed as: (i) conceptually and empirically distinct entities; (ii) separate phenomena, each of which may develop into the other over time; (iii) heterogeneous syndromes that are associated because of shared subtypes; (iv) alternative manifestations of a common underlying predisposition; and (v) different points along the same continuum.  

Antidepressants are the most effective drug treatment both for depression and anxiety disorders; the selective serotonin reuptake inhibitors in particular have been widely used to treat comorbid anxiety and depression, which is the rule rather than the exception in most patients. This points to a common role for the serotonin system in both clinical entities, and there is some evidence to implicate certain serotonin receptors, such as the selective desensitization of 5-HT_1A receptors associated with symptom improvement, or the downstream processes initiated by the action on these systems. The hypothalamic-pituitary-adrenal axis has also been implicated in animal and clinical studies investigating the pathogenesis of anxiety and depression. Some functional brain imaging studies have implicated certain structures in both anxiety and depression. The anterior cingulate cortex in particular has long been recognized as being involved in both cognitive and emotional processing, and it has also been implicated in depression and anxiety disorders such as panic disorder, phobia, post-traumatic stress disorder, and obsessive-compulsive disorder. In controlled clinical studies, depression and anxiety disorders have a significant placebo response and both improve with cognitive behavioral psychotherapy, which in most cases, is administered concomitantly with antidepressant drugs.

Depression and anxiety disorders share a significant nonspecific component that encompasses general affective distress and other common symptoms. General distress, physiological tension, and hyperarousal are more specific to anxiety, and melancholia and pervasive anhedonia are more specific to depression.

References
The question posed, whether depression may exist without anxiety, will not be considered for everyday normal states of sadness, where the mood disturbance is mild, transient, and situational. This discussion is confined to the clinical context where pathological mood is defined by a collection of particularly intense and persistent symptoms that cause significant impairment in overall functioning. Virtually all research on this topic has been confined to major depressive disorder (MDD).

Anxiety is arguably a universal feature of the human condition; it is a natural response to threat or danger. Normal anxiety is usually brief, transient, and understandable in the context of developmental background and current life circumstances. As depressive illness is a significant threat to an individual’s well-being and survival, it is probable that all clinically depressed individuals experience some level of anxiety. However, normal anxiety will not impact adversely on recovery; it may alert the individual of the need to seek treatment, and in fact be lifesaving.

A question of greater relevance is whether clinically significant anxiety is always a constituent of depression. Such anxiety will add to functional impairment and adversely affect outcome. Does “pure depression” exist? Prior to our modern classificatory systems—the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)—depression was often referred to as being either endogenous or reactive. The former was considered mainly an innate illness, relatively free from anxiety symptoms, while the latter was far more common, viewed as emanating from stressful life events that resulted in mixed anxiety and depressive responses. Depression had also been separated into psychotic and neurotic types, the latter suggesting an underlying possibly primary anxiety disorder with a superimposed depressive coloring. These older classifications therefore implied that depression in a pure form might exist. These cases were viewed as being far less common, believed to be essentially biological and to display particular vegetative features such as psychomotor slowing, anorexia, and diurnal variation, possibly with psychotic features. How does modern evidence support this hypothesis?

Several studies have investigated comorbidity in patients with MDD, and these report that up to two-thirds of patients may suffer from a comorbid anxiety disorder. The National Comorbidity Survey Replication study reported that in individuals with MDD, 67.8% had a comorbid anxiety disorder. Clark similarly found that 56% of depressed individuals had a comorbid anxiety disorder. Even if approximately one-third of MDD patients do not have a comorbid anxiety disorder, many of these may experience pathological levels of anxiety that do not reach the level of a disorder. Fawcett and Kravitz found that most patients with MDD experienced symptoms of anxiety, with 72% reporting worrying, 62% psychic anxiety, 42% somatic complaints, and 29% panic attacks. These symptoms were viewed as clinically relevant. Sartorius et al found that approximately 90% of patients with MDD had clinically significant symptoms of anxiety. Hranov estimated that >95% of depressed individuals have at least one symptom of anxiety.

The following conclusions may therefore be made. First, whether anxiety is present in clinical depression has only been substantially investigated in MDD. Whether “pure depression” exists in other forms of depression such as dysthymic disorder, although unlikely, cannot be definitively answered. Normal levels of anxiety are to be expected in all individuals, including those who are depressed. Pathological and clinically relevant anxiety has been shown in the majority of patients with major depression. It is plausible, however, that there do exist rare cases of “pure depression” uncontaminated by pathological levels of anxiety. It is the author’s (IS) clinical experience that this is indeed the case.

References
Anxiety and depression are highly comorbid diseases, with comorbidity particularly important as these are the most prevalent psychiatric disorders. Few therapeutic strategies address anxiety within depression, and those existing are far from being satisfactory in terms of latency of onset, tolerability, and dependence. As Valdoxan has demonstrated efficacy in depression vs placebo and comparators in several clinical trials, and has proven anxiolytic efficacy in animal models, the anxiolytic activity of Valdoxan 25-50 mg was evaluated in depressed patients, including the most anxious ones, in comparison with placebo and selective serotonin reuptake inhibitors (SSRIs)/selective serotonin-norepinephrine reuptake inhibitor (SNRI). Data from 3 short-term placebo-controlled studies and 3 short-term studies vs SSRIs (fluoxetine, sertraline) and SNRI (venlafaxine) in major depressive disorder were assessed according to the anxiety subscore of the Hamilton Depression Rating scale (HAM-D, items 10+11) and the specific anxiety scale, the Hamilton Anxiety Scale (HAM-A), in the total population and in the most anxious depressed patients (anxiety subscore ≥5 in the HAM-D at inclusion). Valdoxan demonstrated antidepressant efficacy in the most anxious patients and an early anxiolytic efficacy from one week of treatment that was significantly greater vs placebo throughout the whole treatment period (6-8 weeks). This efficacy was maintained in patients not treated concomitantly with benzodiazepines. Compared with SSRIs and the SNRI venlafaxine, Valdoxan’s antidepressant and anxiolytic efficacies were greater in the highly anxious patients, by both evaluation methods. Thus, Valdoxan possesses anxiolytic efficacy in depressed patients from the first weeks of treatment, even in those with higher anxiety, and offers a needed alternative to SSRIs/SNRI for patients with comorbid conditions.

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Efficacy of Valdoxan, the first melatonergic antidepressant, in anxiety within depression

by C. Muñoz, France
depression associated with anxiety are significantly more impaired than those without anxiety; comorbid anxiety is associated with higher clinical severity, including suicidal risk and treatment resistance.\textsuperscript{2,6} Recent results demonstrated that after 6 weeks of treatment in partial responders, more severe psychological symptoms of anxiety were associated with both longer time to remission and lower rates of remission.\textsuperscript{7} In the STAR*D study, patients with anxious depression had lower remission rates (22% vs 33%), a worse side-effect profile, and a longer time to remission.\textsuperscript{8} Furthermore, anxiety is a common residual symptom. In this context, anxiety is responsible not only for relapses, but also for functional impairment.\textsuperscript{9}

This comorbidity is particularly important as both pathologies are the most prevalent psychiatric diseases. According to the World Health Organization, depression was the leading cause of disability and the fourth leading contributor to the global burden of disease in 2000,\textsuperscript{10} as measured in disability-adjusted life-years. In particular, unipolar depression is expected to become the second-ranked cause of disease burden in 2020, just behind ischemic heart disease, and will represent one-third of all worldwide disability caused by a neuropsychiatric condition. Furthermore, the new estimates of the analyses performed in the European Union confirm that depression is already the most important single contributor to the total disease burden.\textsuperscript{11} Anxiety disorders comprise different disorders such as generalized anxiety disorders, panic disorder, social phobia, obsessive-compulsive disorder and posttraumatic stress disorder, and these disorders contribute enormously to the burden of the disease.\textsuperscript{12}

The high prevalence of this comorbidity raises the question of whether these clinical conditions should be considered different conditions, albeit often overlapping, or different aspects of the same condition. Thus, the future edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) will consider dimensional aspects of depression and anxiety and among the new categories has added “mixed anxiety/depression disorder” to the entity “depression.” By doing so, the classification better reflects clinical reality, in which most patients have depressed and anxious symptoms. Indeed, the average patient initiating depression treatment is a middle-aged woman, with moderate depression; and 82% of these patients have anxiety symptoms (unpublished observations).

Therefore, the recognition and treatment of comorbid anxiety in major depression is a critical issue, and practitioners need clinically effective antidepressants. However, only a few therapeutic classes have been approved for the treatment of anxiety disorders, and few strategies have been proposed for the treatment of anxiety and depression. First, the adjunction of an anxiolytic agent, typically benzodiazepines, to the antidepressant reduces anxiety in the short term, but can lead to dependence and suicidal or accidental overdose. The preferred approach is to prescribe an antidepressant alone, which reduces symptoms for patients with major depression plus symptoms of anxiety or major depression with comorbid anxiety disorder. The use of monotherapy with an antidepressant in patients with a comorbid diagnosis may help treatment adherence, reduce risk of drug-drug interactions, and be better tolerated. Furthermore, prescribing an antidepressant may facilitate treatment in patients with mixed symptoms when differential diagnosis between depression and anxiety is difficult. Tricyclic antidepressants (clomipramine) have long been approved for the treatment of anxiety disorders as well as depression; however, due to their secondary effects, they are not recommended as first-line treatments. The efficacy of approved serotoninergic antidepressants (paroxetine, sertraline, escitalopram) has been questioned\textsuperscript{13} as selective serotonin reuptake inhibitors (SSRIs) were not found to be superior to other antidepressants in the treatment of anxious depression. Selective serotonin-norepinephrine reuptake inhibitors (SNRI) (venlafaxine, duloxetine) have also been approved for treatment of anxiety disorders and major depression. However, these antidepressants have some disadvantages, such as their latency of onset of action, and they are not equally tolerated by every patient, thus new compounds need to be developed.

Valdoxan, the first melatonergic antidepressant, has proven its efficacy in depression in several controlled trials vs placebo and available comparators in both the short and long term,\textsuperscript{14-21} and this efficacy has been shown to be maintained in the more severely depressed patients.\textsuperscript{21} The antidepressant efficacy of Valdoxan has been demonstrated to have a distinctive profile due to its unique mechanism of action—resynchronization of biological rhythms by the synergy of melatonergic and 5-HT\textsubscript{2C} receptors.\textsuperscript{23,24}

In addition to its antidepressant efficacy, Valdoxan has proven anxiolytic-like activity in appropriate and validated animal models.\textsuperscript{25,26} This activity is also likely to be due to the synergy of melatonergic and 5-HT\textsubscript{2C} receptors.\textsuperscript{26}

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CGI</td>
<td>Clinical Global Impression Scale</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>HAM-A</td>
<td>Hamilton Anxiety Scale</td>
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<tr>
<td>HAM-D</td>
<td>Hamilton Depression Rating scale</td>
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<tr>
<td>HAMD-17</td>
<td>17-item Hamilton Depression Rating scale</td>
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<tr>
<td>LOCF</td>
<td>last observation carried forward</td>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<tr>
<td>SNRI</td>
<td>selective serotonin-norepinephrine reuptake inhibitor</td>
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<tr>
<td>SSRRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>STAR*D</td>
<td>Sequenced Treatment Alternatives to Relieve Depression [study]</td>
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For the above reasons, it was of the utmost interest to explore Valdoxan’s antidepressant effects (evaluated by the Hamilton Depression Rating scale [HAM-D]) in the most anxious patients and its anxiolytic effect on anxious symptoms in depressed patients. Analyses were carried out on data taken from a pool of 3 short-term placebo-controlled studies\(^1\) and a pool of 3 short-term studies vs SSRIs (fluoxetine and sertraline) and the SNRI venlafaxine.\(^2\)\(^3\)

These 6 studies were multicenter, double-blind, randomized trials for Valdoxan in major depressive disorder (MDD). The patient populations in these studies were similar: outpatients fulfilling DSM-IV (fourth revision of the DSM) criteria for MDD, males and females (with a higher proportion of female patients, between 60%-80%), mean age in the early forties, and having an average number of MDD episodes ranging from 2.2-2.9. The studies included patients with HAM-D scores of 20-22 for 5 studies and HAM-D \(\geq 25\) for the study with fluoxetine. The doses of the antidepressants administered were: Valdoxan 25-50 mg (with the exception of one placebo-controlled study, where only the dose of 25 mg was evaluated), fluoxetine 20-40 mg, sertraline 50-100 mg, and venlafaxine 75-150 mg. The doctors and patients were blinded to the increase in dose.

The antidepressant and anxiolytic efficacies were evaluated in the total population and in the more severely anxious patients. The most severely anxious patients were defined as those entering the study with a score \(\geq 5\) for the items of the HAM-D scale reflecting psychic anxiety (item 10) and somatic anxiety (item 11). Antidepressant efficacy was evaluated according to total scores from the 17-item HAM-D (HAM-D-17) and Clinical Global Impression (CGI) scales; anxiolytic efficacy was assessed by the score for items 10 and 11 on the HAM-D scale (for all 6 studies), and by the more specific evaluation tool for anxiety symptoms, the Hamilton Anxiety Scale (HAM-A) (for one of the studies vs placebo over 8 weeks of treatment and in the 3 studies vs comparators over a 6-8 week treatment period).

Analyses of variance were carried out for the 6-8 weeks of treatment using the last-observation-carried-forward method. Meta-analytic methods were used to provide an estimate of the overall treatment effect of Valdoxan as compared with placebo or SSRI/SNRI. The antidepressant efficacy of Valdoxan is stronger in the most anxious patients vs placebo or comparators early in the treatment

In the 3 short-term studies vs placebo, Valdoxan’s antidepressant efficacy was demonstrated after a mandatory period of 6-8 weeks. The patients were also treated with or without concomitant benzodiazepines (only low doses of diazepam, zopiclone, or zolpidem were allowed). In the total population of these pooled studies (358 patients treated with Valdoxan and 363 patients treated with placebo), the difference in the HAM-D total score after the treatment was 2.86 \((P<0.001)\) in favor of Valdoxan 25-50 mg.\(^2\) In the subpopulation of highly anxious patients (222 and 231 treated with Valdoxan and placebo, respectively), the difference was already significant after only 2 weeks of treatment \((\Delta\) after 2 weeks \(=2.25\pm0.54, P<0.001; \Delta\) at end point \(=4.36\pm0.71, P<0.001\) (Figure 1).\(^2\)

The superiority was observed whether or not they were treated with concomitant benzodiazepines.

In the studies vs comparators, the total population included 562 depressed patients treated with agomelatine and 576 treated with SSRI/SNRI. Valdoxan demonstrated its antidepressant efficacy in this population over 6-8 weeks of treatment. The differences after treatment, based on the HAM-D and CGI score, were always in favor of Valdoxan: vs fluoxetine, the differences were 1.49 (superiority study; \(P<0.05\) for the
Valdoxan: demonstrated early anxiolytic efficacy within depression

Evaluation of the 3 placebo-controlled studies demonstrated that the anxiolytic efficacy of Valdoxan also appears early in the treatment of depressed patients: evaluation according to the HAM-D anxiety subscore (sum of items 10+11) shows that from the first evaluation time point (week 2), there was a significant difference in favor of Valdoxan, not only in the total population (Δ = 0.29±0.10; P=0.004), but also in the highly anxious population (Δ = 0.34±0.12; P<0.005) (Figure 2) which was sustained over the course of the treatment (weeks 6-8; P<0.001 for both populations). This efficacy has been demonstrated for psychic as well as somatic anxiety, even in the highly anxious population of depressed patients (Figure 3). This advantage remained significant in patients who did not concomitantly receive benzodiazepines. Over the 6-8 weeks of treatment, Valdoxan demonstrated a major anxiolytic efficacy: for the total population, Δ vs placebo = 0.15±0.08 (P=0.066) and 0.21±0.08 (P=0.009) for psychic and somatic anxiety, respectively; for the patients with high anxiety at baseline, Δ vs placebo = 0.29±0.11 (P=0.006) and 0.27±0.10 (P=0.007), for psychic and somatic anxiety, respectively.

The anxiety symptoms within depression were also evaluated vs placebo using the HAM-A over 8 weeks of treatment in one of the placebo-controlled trials. Valdoxan 25 mg led to a significant decrease in the HAM-A scores in the total population (Δ vs placebo = 3.43±1.18; P=0.011) and in the highly anxious population (Δ vs placebo = 4.68±1.54; P=0.003) at the first evaluation time point (end point). Valdoxan: demonstrated favorable anxiolytic efficacy within depression versus SSRIs and SNRIs

It is of major interest to evaluate the efficacy of Valdoxan, in comparison with available antidepressants, on anxiety symptoms in depressed patients, as SSRIs and SNRIs are far from being satisfactory in terms of effectiveness. Head-to-head trials of Valdoxan vs the more commonly used antidepressants showed an advantage of Valdoxan vs venlafaxine, fluoxetine, and sertraline.
ference in favor of Valdoxan was again demonstrated, as the HAM-A total score was 11.1±8.1 with Valdoxan and 12.3±10 with fluoxetine.20

The meta-analysis of these studies shows a clear advantage of Valdoxan vs these comparator treatments: the comparison of HAM-D anxiety subscores was in favor of Valdoxan (Δ vs comparators =0.20±0.14; P=0.167), as was the significant difference in HAM-A scores (Δ=1.39±0.5; P=0.006) in the total population.27

These advantages persist and are even higher in the highly anxious population. The comparison of HAM-D anxiety subscores yields a difference of 0.26±0.19 (P=0.160) in favor of Valdoxan, and comparison of HAM-A scores yields a difference of 1.72±0.8 (P=0.032), also in favor of Valdoxan (Figure 4).27

**Conclusion**

These data clearly demonstrate that Valdoxan possesses anxiolytic efficacy within depression as early as the first weeks of treatment. Not only are its antidepressant properties maintained in the more anxious patients, Valdoxan also shows anxiolytic efficacy in depressed patients, even those with higher anxiety. Of particular importance are the results obtained in patients not treated with benzodiazepines, which demonstrated that even in the absence of this concomitant medication, Valdoxan alleviated anxiety. Therefore, coadministration of such anxiolytic agents with Valdoxan is unnecessary, thus providing a large number of advantages (no deterioration of daytime condition, no withdrawal syndrome, no dependence, among others).

Of great importance is the favorable effect of Valdoxan in anxiety within depression as compared with SSRIs and the SNRI venlafaxine, even in the more anxious patients, as this offers a much needed alternative for patients with comorbid conditions. As doctors have recognized that more than 80% of depressed patients have anxiety as a comorbidity—implying higher clinical severity, increased suicidal risk, treatment resistance, low rates of remission, and longer time to remission—treatment with Valdoxan ensures optimal management of these depressed patients.

Valdoxan shows a clear advantage vs available antidepressants in addressing the anxious symptoms within depression, and may have a unique position in clinical pharmacotherapy for this comorbidity as it is better tolerated and has better adherence levels than other anxiolytic medications. A recent Valdoxan review21 suggests that because of its unique mode of action—the potential to restore circadian rhythms—Valdoxan might occupy a special place in the management of patients with severe depression and other mood disorders. The results presented in this article support this suggestion and add new insights concerning the properties of Valdoxan, the first melatonergic antidepressant.

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**References**


**Keywords:** anxiety within depression, comorbidity, Valdoxan

**Efficacité de Valdoxan, le premier antdépresseur mélatoninergique, dans l’anxiété liée à la dépression**

L’anxiété et la dépression sont des maladies à forte comorbidity, d’autant plus importante qu’il s’agit des troubles psychiatriques les plus prévalents. Les stratégies thérapeutiques traitant l’anxiété dans le cadre de la dépression sont peu nombreuses et celles qui existent sont loin d’être satisfaisantes en termes de latence de début d’efficacité, de tolérance et de dépendance. Valdoxan ayant démontré son efficacité dans la dépression vs placebo et comparateurs dans plusieurs études cliniques et son efficacité anxiolytique dans des modèles animaux, son activité anxiolytique a été évaluée pour la forme 25-50 mg chez des patients déprimés, y compris les plus anxiens, en comparaison avec un placebo, des ISRS (inhibiteurs sélectifs de la recapture de la sérotonine) et des ISRSN (inhibiteurs sélectifs de la recapture de la sérotonine et de la noradrénaline). Les données issues de trois études à court terme contrôlées contre placebo et de trois études à court terme vs ISRS (fluoxétine, sertraline) et ISRSN (venlafaxine) dans les troubles dépressifs majeurs, ont été évaluées pour l’anxiété d’après les sous-scores de l’échelle Hamilton pour la dépression (HAM-D, items 10 et 11) et d’après l’échelle Hamilton spécifique de l’anxiété (HAM-A) pour la population totale et chez les patients déprimés les plus anxieux (sous-score pour l’anxiété ≥ 5 à l’inclusion pour l’HAM-D). L’efficacité antdépressive de Valdoxan a été démontrée chez les patients les plus anxieux avec une efficacité anxiolytique précocé après 1 semaine de traitement significativement plus élevée vs placebo pendant toute la période de traitement de l’étude (6-8 semaines). Cette efficacité est maintenue chez les patients non traités simultanément par benzodiazépines. Comparé à la venlafaxine (ISRSN) et aux ISRS, Valdoxan a montré, d’après les deux méthodes d’évaluation, une efficacité antdépressive et anxiolytique plus importante chez les patients les plus anxieux. Valdoxan est donc efficace sur l’anxiété chez les patients déprimés dès les premières semaines de traitement, même chez les plus anxieux, et se présente comme une alternative nécessaire aux ISRSN/ISRS pour les patients souffrant de comorbidités.
Anxiety and depression are prominent symptoms in clinical practice and are the basis for the two diagnostic categories, anxiety disorder and depressive disorder, that are sometimes combined in a third: mixed anxiety and depressive disorder. Indeed, the main problem for the clinician and researcher is the somewhat blurred boundary between normal and morbid psychological experience, on the one hand, and between anxiety and depression, on the other. Comorbidity is high in anxiety and depressive disorders, and higher still when viewed long-term, with anxiety tending to predominate at younger ages and depression and somatization developing later. The distinctive quality of the affect is important in differentiating normal experience from anxiety and depressive disorders. Morbid anxiety and morbid sadness are “vital feelings”; as described by Scheler, Schneider, and López-Ibor Sr, they are characterized by “embodiment” and nondependence on external circumstance. Evolutionary theory offers useful insights into the possible adaptive value of the feelings of anxiety and sadness. Feelings may aid clinicians in classifying certain states of mood as “normal” or “pathological” and guide them to more appropriate decisions.

Prof López-Ibor, as one of the major figures in psychiatry in Spain, could you tell us the highlights of your career?

Just as my father followed his two elder brothers into medicine, so I followed my father into psychiatry, in which, I suppose you could say, we have formed a mini-dynasty in the Spanish setting. We even have the same initials, which complicates life for bibliographers! My father was born in 1908, and completed his specialist training in Zurich, Berlin, Paris, and Tübingen. This background enabled him to bring Spanish psychiatry firmly into the European loop, via the Spanish Psychiatric Society and the journal Actas Luso-Españolas de Neurología, Psiquiatría y Ciencias Afines, both of which he cofounded. Intellectually, I would describe myself as his successor. I have approached psychiatric illness in the same tradition, with particular respect to anxiety and depression disorders. My father was at pains to emphasize a biological and evolutionary interpretation of the common syndromes, distancing himself from Freud in that regard, despite the initial attraction that had first drawn him to the specialty. For example, I believe that his description of vital anguish, published in his book of the same title, remains largely valid today, despite dating from 1950.
How do you view the relationship between anxiety and depression?

It’s extremely close. These are among the two most common complaints encountered at both the primary care and specialist levels. They are the backbone of two diagnostic categories, anxiety disorder and depressive disorder, that we frequently find combined in a third: mixed anxiety and depressive disorder, enshrined in the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10), and most probably in the forthcoming fifth revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).

Anxiety is the feeling prompted by an as yet unidentified threat or danger. It consists of increased alertness and exploratory attention, and an emotional readiness for fight or flight. Depression is the feeling that arises from the experience of loss.

Since a threat, such as severe disease in a beloved person, may be followed by actual loss (such as death), it is quite common for depression to follow an anxiety state. But the reverse also happens, as when a patient may feel hopeless, helpless, and hapless during a depressive episode, with the result that minor circumstances become highly threatening.

The lifetime combination of anxiety and depressive disorders is also common. We conducted a near 50-year follow-up study of 370 patients diagnosed with anxiety disorder between 1950 and 1961. Two-thirds were rediagnosed according to DSM-III-R (DSM, third edition, revised) criteria as suffering from panic disorder and the rest from generalized anxiety. On the whole, there is a common natural history starting with school phobia in childhood (more prevalent in panic disorder patients), followed by anxiety in the 20s and 30s, depression in the 40s and 50s, and somatization disorders thereafter. Interestingly enough, this is the same pattern as presented by one of Freud’s most celebrated patients, the Wolf Man.

The promotion of these two feelings, anxiety and depression, to the rank of diagnostic categories raises the issue of the frontier between normal and pathological psychological experience. Their frequent coexistence raises a second problem: that of the exact differences between anxiety and depression. Such as medicalizing normal suffering, interfering with normal psychological processes, and creating dependence on prescription drugs, the health system and/or on the physician him/herself. Clinicians should also be at pains to avoid cosmetic psychopharmacology, by which I mean dealing with health as if it were just another consumer item.

In other words, failure to give due consideration to the above two problems can lead the clinician to take important decisions on the basis of inaccurate diagnosis. The danger is urgent and real: mood (affective) disorders attract the lowest inter-rater reliability scores in ICD-10 field trials. It is important to go beyond purely symptomatic aspects into a more comprehensive approach to the understanding of anxiety and depression. This goal may be achieved by integrating insights from the spiritual, philosophical, and neurobiological literature.

Can you illustrate the dangers of a purely symptom-based approach?

Current classification systems in psychiatry can lead to confusion if clinicians fail to realize that classifications are not treatises of psychopathology, defining what illnesses are. Nor must diagnostic criteria be confused with symptoms, or symptoms with illnesses. For instance, two patients displaying identical symptoms (eg, depressive mood during most of the day and most days; marked reduction of appetite; insomnia; and psychomotor inhibition) attract different diagnoses—major depressive episode or bereavement—according to DSM-IV-TR (DSM, fourth edition, text revision) depending on whether or not they are associated with the loss of a beloved relative or friend.

DSM-5 is considering dropping the exclusion criterion of grief for diagnosing major depression, a step wrongly interpreted by some as converting (normal) bereavement into a clinical disorder; as a member of the DSM-5 Mood Disorder Work Group has recently argued, the diagnosis of major depression requires the presence of a set of clinical manifestations, regardless of whether the patient has or has not recently lost a beloved relative.

<table>
<thead>
<tr>
<th>SELECTED ABBREVIATIONS AND ACRONYMS</th>
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<tr>
<td>DSM</td>
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Comparative psychopathology appears to have been one of your abiding interests

Indeed. One consequence of the difficulty in clarifying the significance of anxiety and depression is the variable worldwide prevalence of the clinical disorders concerned. Take the example of depressive disorder, which shows large and unexplained international differences. The prevalence of major depressive episode oscillates between over 3500 per 100,000 inhabitants per year among women in the World Health Organization (WHO) region of the Americas, to under 1500 among Western Pacific Region men.

In primary health care, the differences are even more striking: depression accounts for around 30% of consultations in Santiago de Chile, but under 3% in Nagasaki. The differences reported by the WHO between cities such as Buenos Aires and Santiago de Chile or between London and Padua are, strictly speaking, inexplicable.  

In a more general sense, the steady increase in the incidence and prevalence of mental disorders conveys the impression that psychiatry is ineffective at the public health level. When dealing with such widely prevalent disorders, I think an alternative approach could be important. Rather than investigating the causes of depressive disorder, it might be more useful to determine instead why certain individuals are spared.

The prevalence of negative affect appears disproportionate: 15% of the US population has had an episode of severe depression, while many others simply have frequent bad days when they are too worried, sad, or angry to function, or at least nowhere near being full of energy and loving well-being. Most attempts to understand this state of affairs seek explanations in individual differences, often based on the assumption that there is something wrong with those affected.

Is this where we come back to the difference between normal and pathological anxiety and depression?

The first systematic attempt to differentiate (normal, everyday) sadness from depression took place 100 years ago in continental Europe when the sadness present in depression was shown to have a distinct quality that could be identified in clinical settings and used as a basis for diagnosing (morbid) depression. This distinctness has been variously characterized as a lack of subjective response (blunting, affect anesthesia), behavioral withdrawal (inhibition), and altered vitality (vital sadness), associated with the presence of somatic symptoms, absence of motivation, and anhedonia. It is also interesting to note that observers are able to perceive this distinct quality despite patients often having considerable difficulty in verbalizing differences from normal sadness (a semantic factor that can be a source of diagnostic error). The psychiatrist Kurt Schneider (1887-1967) introduced the concept of vital sadness as a disturbance of vital feelings, based on the description by the philosopher Max Scheler (1874-1928) of four types of feelings:

i) Sensory feelings (sinnliche Gefühle) or emotional or sensation feelings (Empfindungsgefühle) involving specific parts of the body, such as pain, a knot in the stomach from hunger, or spine-chilling fear.

ii) Vital feelings (Lebensgefühle) or body feelings (Leibgefühle) involving body experience as a whole, such as distress or well-being.

iii) Psychic feelings (seelische Gefühle) or pure ego feelings (reine Ichgefühle), corresponding to the environment and external world. They are reactive to external circumstances such as joyfulness, enjoyment, sadness, or despair.

iv) Spiritual feelings (geistige Gefühle) or personality feelings (Persönlichkeitsgefühle), such as ecstasy or agony that are spontaneous and absolutely beyond specific values.

In summary, vital sadness is experienced independently of external circumstance as a negative subjective experience of one’s body, which is felt as weighty, slow, unpleasant, or painful, while normal (reactive) sadness is directly related to negative circumstance.

Similarly, López Ibor Sr concluded that the anxiety characterizing neurotic disorders was a vital rather than psychic or reactive feeling.  

This introduced the concept of “vital anxiety,” thereby paving the way for the biologic treatment of this group of disorders (ie, monoamine oxidase inhibitors for anxiety, and clomipramine for obsessive neurosis, as I proposed in the early ’70s).

You have also drawn attention to more recent Spanish contributions on this topic

Ramos Brieva et al carried out a series of controlled studies over two decades. Using discriminant analysis to determine how patients define pathological sadness, they developed a Pathological Sadness Index with a sensitivity of 0.94, specificity of 0.96, and total misclassification rate of 5% \( (\kappa_w=0.90) \). They found two factors that accounted for 55% of total variance (construct validity): “distinct quality” and “embodiment.” The presence of “distinct quality” was independent of the presence or absence of a life event and more frequent in melancholic subjects. The Pathological Sadness Index showed “distinct quality” in 83% of cases without subjective experience of sadness.

The same authors reanalyzed the Newcastle data of Kiloh and Garside and Carney et al. They studied the influence...
of the “distinct quality” item on core depressive symptoms. Removal of the influence of this item deprived the depressive syndrome of its original cohesion, suggesting that the “distinct quality” could be the agglutinative component of core depressive symptomatology.\(^\text{16}\) In other studies Ramos Brieva et al addressed the issue of vital anxiety.\(^\text{16}\) Discriminant analysis of the description of the anxiety experienced by subjects with panic attacks and control subjects with common fear showed the existence of qualitative differences between both experiences. The difference was also present in the sadness reported by patients with anxiety disorders.

**How does evolutionary theory help in understanding emotion?**

Experience and emotional behavior are so varied and omnipresent in human beings and animals that they must play an important role in individual and species survival. The philosopher Sartre considered emotion as an instance of the replacement behavior (Ersatzpsychologie) that appears when objectively guided behavior is not possible.\(^\text{17}\) Given the impossibility of facing too rational a world, as after the loss of a significant other, emotion establishes a new relationship with the world in which the apparently non-adaptive withdrawal reaction makes sense. Affective reactions have a significance that is not rational, but symbolic and magical.

The most appropriate strategy for differentiating normal from pathological mood states takes its inspiration from evolutionary theory by addressing the following two questions: i) what concerns a particular person visiting a psychiatrist?; and ii) what are the public health consequences of defining a boundary between normal and pathological?

Evolutionary theory helps to explain why disease is so prevalent and difficult to prevent. Human genetic variations that increase resistance to disease often have costs, while some variations that increase vulnerability can have benefits. Take the classic example of sickle cell anemia. Is it “normal”? The answer is that it depends on where the person lives, given that those with sickle cell anemia are better able to resist malaria than those without.

Functionalist consider that emotions evolved for particular functions, such as to keep the subject safe.\(^\text{18}\) Natural selection has shaped emotions so that they adjust various aspects of the organism to provide selective advantage in particular kinds of situations. Emotions are designed to maximize reproductive success rather than happiness. Negative emotions such as anxiety and low mood are defenses that have evolved from conflicts inherent in social life. Emotions are valenced because selection shapes special processes for situations that have influenced fitness in the past.\(^\text{19,20}\) In situations that decrease fitness, negative emotions are useful and positive emotions harmful.

**An emotion that confers evolutionary advantage can hardly be described as abnormal**

Just as there are positive aspects to (normal) anxiety, namely, the subjective experience of threat and the preparation for fight or flight, we should assume that depression also has adaptive value. Indeed, sadness has positive functions: it increases the ability to confront adaptive challenges when the effort to achieve an important goal may expose to danger, loss, harm, or the pointless expenditure of energy. Sadness also communicates a need for help. It shields the individual from hierarchical conflict by inhibiting aggression towards rivals and superiors. It promotes compromise in striving for unreachable goals, modulates interventions, and may lead to the recovery of lost relationships. Depressive feelings increase a person’s sensitivity to the suffering of others, thereby enhancing the survival of the kinship group and, by extension, that of the species. Just as negative emotions are an advantage in threatening situations, positive emotions aid in situations that offer opportunity or when progress toward a goal is faster than expected. We need to challenge the common notion that positive and negative emotional states are simple opposites.

One of my special interests is the mood disorder cyclothymia, with particular respect to creativity. The pursuit of romantic opportunities in cyclothymia suggests that this condition may have evolved as a mechanism for reproductive success. The cyclothymic creative bent as expressed in poetry, music, painting, cooking, and fashion design (among men, in particular) also appears useful for sexual seduction. Hyperthymic traits lend distinct advantage in leadership, exploration, territoriality, and mating. Selected aspects of this hypothesis have been tested using correlations between the constituent traits of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEPMS) scale and the Temperament and Character Inventory (TCI).\(^\text{21}\)

**A final word?**

Anxiety and depression are feelings, that is, psychological experiences, but not only that. Feelings go together with somatic manifestations, specific gestures and expressions, and behaviors such as crying or shouting for help. The somatic manifestations of anxiety are stress reactions. They are neurohumoral reactions to stressors that are triggered as nonspecific mechanisms for confronting actual or threatened imbalance of the milieu intérieur or homeostasis.

Depressive reactions are more difficult to characterize, but go along with the findings of chronic stress. The neurobiology of depression resembles hibernation, in other words, a state of drowsy withdrawal in which key physiological and biochemical activities are suppressed and energy consumption turned down to its lowest setting, as a survival strategy under extreme environmental conditions.
ANXIÉTÉ ET DÉPRESSION AUJOURD’HUI : QUELLE EST VOTRE EXPÉRIENCE PERSONNELLE ?

L’anxiété et la dépression, symptômes de premier plan en pratique clinique, sont la base de deux catégories diagnostiques, les troubles anxieux et dépressifs parfois associés dans une troisième catégorie : les troubles mixtes anxio-dépressifs. Bien sûr, le principal problème du médecin et du chercheur est cette frontière un peu floue entre un côté un vécu psychologique normal et pathologique et de l’autre côté l’anxiété et la dépression. La comorbidité des troubles anxieux et dépressifs est élevée et l’est encore plus à long terme, l’anxiété prédominant aux âges plus jeunes et la dépression et la somatisation se développant plus tard. L’aspect distinctif de l’affect est important pour différencier un vécu normal des troubles anxieux et dépressifs. L’anxiété et la tristesse moribondes sont des « sentiments vitaux » ; Scheler, Schneider et Lopez Ibor Sr les décrivent comme une expérience de « embodiment (incorporation) » et une non-dépendance vis-à-vis des circonstances extérieures. La théorie de l’évolution nous éclaire sur la valeur adaptative potentielle des sentiments d’anxiété et de tristesse. Les sentiments peuvent aider les médecins à classer certains états d’humeur comme « normal » ou « pathologique » et les orientent pour prendre de meilleures décisions.

Keywords: anxiety; depression; evolutionary theory; mood; normal and pathological psychological experience
Although the prevalence of anxiety and depressive disorders among community-residing older adults is lower than in middle-aged persons, there are high rates of both in older people admitted to general hospitals, those receiving domiciliary care, and those residing in nursing homes. High rates of anxiety and depression also occur in older people with mild cognitive impairment and dementia. Evidence-based psychological and pharmacological treatments are available for the treatment of anxiety and depressive disorders in older people. These two treatment modalities show approximately equivalent efficacy, although drug treatments are generally preferred for older people with more severe depression and psychological treatments are generally preferred for older people with mild to moderate anxiety. Both interpersonal psychotherapy and cognitive behavioral therapy are effective in older people, although the latter is in more widespread use. Rational drug treatment of anxiety and depression in older people mainly involves the use of antidepressant medication, particularly the selective serotonin reuptake inhibitors. At present, it is unclear whether antidepressant medication is effective in patients with both dementia and depression. Electroconvulsive therapy remains an appropriate option for older depressed patients who have stopped eating or drinking, have psychotic symptoms, or are actively suicidal. Combination treatment with antidepressant medication and one of the psychological treatments is recommended although there is only limited supporting evidence in older people. Newer brain stimulation treatments such as transcranial magnetic stimulation are being trialed in older people with anxiety and depression, but in many places their use remains investigational. Prevention of both anxiety and depression in older people does seem feasible and a stepped-care program has shown promising results.

Background

With increasing longevity in developed and most developing countries, both the proportion and the absolute number of older people are rising worldwide. Sex-specific mortality rates mean that population aging is accompanied by demographic feminization. This effect, in combination with cognitive aging, is likely to lead to increased rates of both anxiety and depression. However, in most national epidemiological studies, anxiety and depression fall in prevalence among community-residing individuals after the age of about 50 years (see Figure 1 page 340). The full explanation for this observation is yet to be elucidated,
although selective mortality of people with anxiety and depressive disorders and changes in personality with advancing age are likely to contribute. Although personality is relatively stable over the adult lifespan, older adults do have lower neuroticism in comparison with younger adults. As neuroticism is the character trait most relevant for the development of anxiety and depression, it makes intuitive sense for the prevalence of these two disorders to decrease in late life. Despite these general observations, the trend toward lower rates of anxiety and depression in community-residing older people masks much higher rates of anxiety and depression among hospitalized older people, among those receiving domiciliary nursing care and those living in nursing homes. These individuals are rarely included in national epidemiological surveys. For example, in long-term care (nursing home) settings, the median prevalence of depressive symptoms was found to be 29%, while that of major depressive disorder was found to be 10%. The most prevalent anxiety disorder in older people is generalized anxiety disorder (GAD). Simple or situational phobias also occur commonly, but most national surveys do not measure the prevalence of these due to the difficulty in establishing their clinical significance at cross-sectional interview. Less common anxiety disorders in late life include panic disorder, agoraphobia, social phobia, posttraumatic stress disorder, and obsessive-compulsive disorder. It has been proposed that the sympathetic nervous system becomes less responsive in old age, making panic attacks and panicky feelings less likely. The most prevalent depressive disorder in older people is major depressive disorder. Suicide rates are increased in older people with anxiety and depressive disorders and in many countries this is particularly true for older men.

Comorbidity

Although anxiety and depressive disorders can usually be distinguished from one another in older people, there is substantial comorbidity between the two. This likely reflects shared etiological factors, including polygenic influences, trait neuroticism, childhood adversity, adult adverse life events, physical illness, substance abuse, effects of medication, and cognitive impairment. It also reflects to some extent an overlap in symptoms, particularly between major depressive disorder and GAD. In addition, many older people have subthreshold mixtures of anxiety and depressive symptoms, which warrant the use of the rubric “mixed anxiety and depression.”

The prevalence of substance use disorders declines markedly in later life. This appears to be due to the combined effects of reduced income, reduced tolerance to the effects of alcohol and other drugs, and social disapproval. However, those older people with substance use disorders do commonly have an anxiety and depressive disorder as well. This is particularly true for abuse and dependence syndromes involving alcohol and prescribed hypnotesatives. Anxiety and depressive symptoms also occur commonly in older people with general medical conditions, including chronic obstructive lung disease, ischemic heart disease, and stroke. Because most anxiety and depressive disorders develop before middle age, older persons developing anxiety or depression for the first time in later life must be investigated for an underlying general medical condition. The prevalence of cognitive problems, including mild cognitive impairment and dementia, rises exponentially with advancing age. Both mild cognitive impairment and dementia are associated with high rates of anxiety and depressive symptoms and disorders.
The majority of older people with anxiety and depression are seen in primary care settings. Where this is not the case, the assessment and management of an older person should be undertaken in collaboration with his or her general practitioner (primary care physician) because of the strong nexus between mental health and physical health in older people. A physical examination with special emphasis on neurological and cardiovascular function is recommended as part of the routine work-up.

It is important to check cognitive function in older people presenting with anxiety and depressive symptoms. Cross-sectional assessment of cognitive function is not complete in the absence of an informant interview, as many older people are not aware of the extent of their cognitive impairment. In addition, cognitive screening tests, other than the Informant Questionnaire for COgnitive Decline in the Elderly (IQCODE), do not establish the extent of cognitive change over time. Screening cognitive testing should be undertaken wherever practicable. There are many suitable scales available, including the Addenbrooke’s Cognitive Examination–Revised (ACE-R), which combines items similar to those in the Mini Mental State Examination (MMSE) with items that cover a broader range of brain functions.

It is often useful to obtain a quantitative estimate of the subjective severity of anxiety or depression using rating scales specifically developed for use in older people. Although several scales are now available, the most accessible are the Geriatric Depression Scale and the Geriatric Anxiety Inventory. Both are also available in 5-item short forms for rapid screening in general medical settings.

Investigations
General medical problems become more common with advancing age and must be excluded as potential causes and complications of anxiety and depression. Clinical judgment is required in ordering laboratory investigations and neuroimaging studies. However, the following blood tests are commonly requested: full blood examination, serum electrolytes, serum glucose, serum urea and creatinine, liver enzymes, thyroid stimulating hormone, serum vitamin B12, red cell folate and serum vitamin D. Magnetic resonance imaging is generally considered the neuroimaging study of choice in older people because of its ability to reveal the extent of white matter ischemic changes, although it is often more expensive and less accessible than computer tomographic brain imaging.

Treatment
General measures
The excessive use of caffeine-containing beverages, including coffee and cola drinks, is associated with clinically significant anxiety symptoms in vulnerable individuals. Although these substances are used less frequently in older people, they still occasionally act as exacerbating agents. In addition, excessive alcohol consumption is often associated with depressive symptoms, and withdrawal from alcohol is often associated with both anxiety and depressive symptoms. As a consequence, the initial management of depression or anxiety in older people should include consideration of their caffeine and alcohol intake. Use of amphetamines, cocaine, and narcotics is much less prevalent in most older populations, but is still worth considering in selected cases.

Many general medical conditions are associated with anxiety or depression, including ischemic heart disease, stroke, asthma, emphysema, diabetes mellitus, cancer, Alzheimer’s disease, and virus infections. Prescribed medications can lead to syndromal or subsyndromal depression or anxiety. Commonly implicated agents include corticosteroids; interferon; agents used in the treatment of cancer, such as interleukin 2; and agents used in the treatment of autoimmune disorders, such as tumor necrosis factor α. Sympathomimetic agents, including those used in treatment of asthma and chronic obstructive lung disease, commonly lead to anxiety symptoms. Thus, the management of anxiety and depression in older people should include consideration of any comorbid general medical disorders and any prescribed medication.

There are several nonspecific interventions that are likely to assist many older people with anxiety or depressive disorders; these include psychoeducation, sleep hygiene, and relaxation training. In addition, it is prudent to optimize cognitive function as part of a broader treatment plan for anxiety and de-

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**Selected Abbreviations and Acronyms**

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<th>Abbreviation</th>
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<tr>
<td>ACE-R</td>
<td>Addenbrooke’s Cognitive Examination–Revised</td>
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<td>CBT</td>
<td>Cognitive behavior therapy</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies–Depression</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual for Mental Disorders, fourth edition</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalized anxiety disorder</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Improving Mood Promoting Access to Collaborative Treatment</td>
</tr>
<tr>
<td>IPT</td>
<td>Interpersonal psychotherapy</td>
</tr>
<tr>
<td>IQCODE</td>
<td>Informant Questionnaire for COgnitive Decline in the Elderly</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>PROSPECT</td>
<td>PRevention Of Suicide in Primary care Elderly: Collaborative Trial</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV axis 1 disorders</td>
</tr>
<tr>
<td>SSRRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
</tr>
</tbody>
</table>

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pression in older people. This will often involve the cautious cessation of medications with anticholinergic or antihistaminic effects, which may impair cognition. Because benzodiazepines and related medications also have significant amnestic effects, their use should be minimized in older people.

Most treatments for anxiety and depression in older people can be carried out in primary care settings by appropriately trained general practitioners, clinical psychologists, and nurse practitioners. Cases of diagnostic uncertainty, treatment resistance, or high severity should be referred for specialist attention. Evidence from adult populations indicates that combination treatment with antidepressant medication and a psychological intervention works best, both during acute treatment and for relapse prevention. It is beyond the scope of this article to discuss the management of individual anxiety disorders.

**Drug treatment**

Although benzodiazepines are in widespread use for the treatment of anxiety symptoms and anxiety disorders in adults of all ages, they have a number of disadvantages. First of all, their efficacy has been demonstrated only in short-term studies and it is likely that they actually increase anxiety symptoms in the longer term through withdrawal effects and by limiting environmental exposure. Secondly, they are associated with falls, amnesia, disruption of sleep architecture, and confusion. Thus, if benzodiazepines are to be used, they should be reserved for short-term use, while initiating antidepressant therapy and planning psychological treatment.

Antidepressants are the preferred pharmacological treatment for both anxiety and depressive disorders in older people. There is little evidence to suggest that one antidepressant is superior in efficacy to another, so choice of agent is made mainly on the basis of past history of response and expected adverse effect profile. Some antidepressants are more acti-vating whereas others are more sedating and these properties enable them to be tailored to treat patients with psychomotor retardation or agitation, respectively. The selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for both anxiety and depressive disorders in older people. Commencement of SSS treatment is commonly associated with an initial increase in jitteriness, anxiety or insomnia. This early worsening can be managed with a combination of psychoeducation and the short-term use of a benzodiazepine, such as oxazepam. While generally safer than tricyclic antidepressants and monoamine oxidase inhibitors, the SSRIs are associated with an increased risk of bleeding, hyponatremia, and falls in older people. Hyponatremia appears to occur more commonly in women and those on thiazide diuretics. Citalopram and escitalopram have been reported to be associated with prolongation of the electrocardiogram corrected QT (QTc) interval and cardiac arrhythmias in older people. As a consequence, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) has recommended that citalopram be used in doses no greater than 20 mg daily and that escitalopram be used in doses no greater than 10 mg daily in people aged 65 years and over. By convention, older patients with insomnia as part of their anxiety or depression have been treated with more sedating antidepressants such as fluvoxamine or mirtazapine, which rely on antihistaminic properties to assist with sleep. However, newer drugs such as agomelatine, which work on the melatonergic and 5-HT2C systems, might offer an advantage in this situation. In older people with cognitive impairment, urinary hesitancy, or narrow-angle glaucoma, it is prudent to avoid antidepressants with significant anticholinergic effects, such as paroxetine, the older tricyclics, and monoamine oxidase inhibitors. However, if a tricyclic antidepressant is to be used to treat an anxiety or depressive disorder in late life, it is often preferable to use nortriptyline, as it seems to be associated with the best safety profile in older people. Low-potency antipsychotic medications, such as quetiapine, have sometimes been used in the management of anxiety symptoms. However, there is limited evidence for their use in older people. A meta-analysis of 9 short-term clinical trials of medication for the treatment of GAD in older people found that medication was superior to placebo with a pooled odds ratio of 0.32 (95% confidence interval [CI], 0.18-0.54). Antidepressants, benzodiazepines, and quetiapine all demonstrated short-term efficacy.

**Augmentation strategies**

Combined treatment with antidepressant medication and manual-based psychotherapy (cognitive behavior therapy [CBT] or interpersonal psychotherapy [IPT]) has been shown to improve efficacy both in the acute phase and during relapse prevention in major depression. It is likely that the same combination would also be associated with improved efficacy in the management of late-life anxiety disorders, although no methodologically sound clinical trials of combination treatment have been published. Other augmentation strategies for major depression include the use of mood stabilizers, such as lithium carbonate, sodium valproate, or an atypical antipsychotic. Although carbamazepine can also be used as an antidepressant augmentation agent, its multiple drug-drug interactions make it less suitable for use in older people. Lithium carbonate can be used as an augmentation agent in the acute treatment of major depression as well as in relapse prevention, including following a course of electroconvulsive therapy (ECT). The evidence base for combinations of antidepressants as an augmentation strategy is less secure in older people and best avoided. There is evidence for the use of thyroid hormone as an augmentation strategy in adults, although this must be approached cautiously as there are significant potential adverse effects, particularly in older people.

**Complications of drug treatment**

While the use of antidepressant medication is an important component of the treatment of both anxiety and depression
in older people, it is often associated with adverse effects. A recently reported cohort study found increased mortality among older people treated with modern antidepressants, although confounding by indication might explain at least some of this effect. Importantly, the use of SSRIs to treat depression is associated with a reduced rate of suicide in older adults. Reduced bone mineral density together with an increased rate of falls and fractures has been reported in older people on antidepressant medication, including SSRIs. Hyponatremia also occurs commonly, particularly among older women on diuretic treatment. A large UK clinical trial has suggested that antidepressants might not be effective for the treatment of major depression in the context of dementia. However, this study did have methodological limitations, including the inclusion criterion of a score of 8 or more on the Cornell Scale for Depression in Dementia, rather than a formal diagnosis of major depression based on a diagnostic interview. Hence, the findings should not be taken as the last word on the treatment of depression in dementia. Because the use of antidepressants and other drugs to treat anxiety and depression in later life is often associated with dose-limiting adverse effects and modest efficacy, there may be a role in the future for pharmacogenomic assessment to help with the selection of antidepressant medication and dose range.

**Psychotherapy**

Psychological interventions are often preferred in older people with mild to moderate anxiety or depression. In relation to anxiety, there is evidence for the use of CBT. In relation to depression, there is evidence both for the use of CBT and for IPT. Some modifications are often needed when applying CBT in later life. These have been described in detail in specialist texts. Common modifications include increasing the font size in manuals to allow for visual impairment, increasing the number of sessions to allow for more summary and review work, and incorporating explicit learning and memory aids. In older people with mild cognitive impairment or dementia, the use of cognitive strategies can be quite challenging. In such cases, the clinician can employ the behavioral components of CBT alone. Relaxation techniques, behavioral activation, pleasant event scheduling, and exposure are all worth pursuing. Critical to the success of most behavioral interventions for anxiety disorders in older people is the use of explicit measures to overcome avoidance behavior. CBT and IPT are generally more effective when administered on an individual rather than a group basis. A meta-analysis of CBT for GAD in older people identified 11 small clinical trials with usable data and found that CBT was superior to control conditions with a pooled odds ratio of 0.33 (95% CI, 0.17–0.66).

Most of the available evidence indicates that IPT has satisfactory efficacy in the treatment of depression in older people and is generally well accepted in this age group. IPT is associated with improved outcomes for older depressed patients with cognitive impairment and with reduced caregiver burden. Research in middle-aged persons has demonstrated that IPT and CBT have similar efficacy. Despite these positive findings, IPT does not appear to be in widespread use for depression or anxiety in older people.

**Stepped care**

In the IMPACT study (Improving Mood Promoting Access to Collaborative Treatment), 1801 US primary care patients aged 60 years and over with SCID/DSM-IV (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition) major depressive disorder, dysthymic disorder, or both, were randomized to a 12-month collaborative care intervention or to usual depression care. The collaborative care program involved a depression care manager, a primary care physician, and a psychiatrist, who provided psychoeducation, behavioral activation, antidepressants, problem-solving therapy, and relapse-prevention strategies. The IMPACT intervention was found to be superior to usual depression care at 12-month, 18-month, and 24-month follow-up. The findings from this study suggest that a multimodal, stepped-care approach can be effective for the management of depression in older people.

**Brain stimulation**

ECT is used to treat severely depressed older people and is highly effective in this context. It can be lifesaving in older people who are not eating and drinking, who are psychotic, or who are actively suicidal. ECT is generally well tolerated, apart from causing amnesia, which can take several weeks to resolve. Unfortunately, ECT remains a highly stigmatized treatment modality and it can be difficult to access in some places. Other methods of brain stimulation are gradually gaining clinical acceptance although none has the evidence base of ECT. These methods include transcranial magnetic stimulation (TMS), vagal nerve stimulation, and deep brain stimulation. At present, vagal nerve stimulation and deep brain stimulation are generally reserved for those with severe treatment-resistant disorders unresponsive to multiple courses of treatment, including ECT. TMS is in more widespread use and has the advantage over ECT that no general anesthetic is required. However, the available evidence suggests that ECT has greater efficacy than TMS.

**Prevention**

There is no known method for the universal, population-wide prevention of anxiety or depression in older people. However, there is some evidence for the indicated prevention of depression and anxiety in those showing early symptoms. A Dutch prevention study investigated 170 older primary care patients aged 75 years and over (mean age 81.4 years; 77% female) considered to be at high risk of anxiety or depressive disorder. Participants had a Center for Epidemiologic Studies–Depression (CES-D) scale score of 16 or greater (mean baseline CES-D score, 21.6), but did not have a current MINI (Mini International Neuropsychiatric Interview)/DSM-IV depres-

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*Focus*

Anxiety and depression in late life – Byrne

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sive or anxiety disorder. They were randomized to routine primary care or to stepped care. Stepped care consisted of 3-month cycles of watchful waiting, bibliotherapy, problem-solving treatment, and antidepressant medication provided over a 12-month period. The intervention halved the 12-month incidence of depressive and anxiety disorders with a number-needed-to-treat of 8.3 and at a cost (in 2007 euros) of €4297 per depression- and anxiety-free year.

There is also evidence for the selective prevention of depression in specific contexts, including macular degeneration. In a US study, 226 older people (mean age 81 years) with neovascular macular degeneration were randomized to usual care or 6 sessions of problem-solving treatment over 8 weeks.

Problem-solving treatment was associated with a 50% reduction in incident depression at 2-month follow-up. The evidence for prevention of completed suicide in older people is meager, although the PROSPECT study (Prevention Of Suicide in Primary care Elderly: Collaborative Trial) demonstrated some reduction in suicidal ideation in older depressed people treated with antidepressants and/or psychotherapy.

**Conclusion**

Anxiety and depressive disorders are not uncommon in later life and frequently complicate the common medical problems of later life. Many patients can be treated successfully with psychotherapy alone or with antidepressant medication in combination with psychotherapy.

**References**


**Keywords:** antidepressant; anxiety; augmentation strategy; brain stimulation; combination therapy; depression; elderly; psychological intervention; stepped care
Bien que la prévalence des troubles dépressifs et anxieux soit plus faible chez les sujets âgés non-hospitalisés que chez les sujets d’âge moyen, ces deux pathologies sont très souvent retrouvées chez les sujets âgés à l’hôpital, chez ceux qui sont soignés à domicile et chez ceux qui sont en maison médicalisée. Des taux élevés d’anxiété et de dépression surviennent également chez les sujets âgés atteints de troubles cognitifs légers et de démence. Des traitements pharmacologiques et psychologiques basés sur les preuves sont disponibles pour les troubles anxieux et dépressifs de la personne âgée. Ils ont à peu près la même efficacité, les traitements pharmacologiques étant généralement réservés aux sujets plus âgés souffrant de dépression plus sévère et les traitements psychologiques aux sujets plus âgés souffrant d’anxiété légère à modérée. La psychothérapie interpersonnelle et la thérapie cognitive comportementale sont efficaces toutes les deux chez les personnes âgées bien que la dernière soit plus volontiers utilisée. Le traitement pharmacologique rationnel de l’anxiété et de la dépression des personnes plus âgées est basé principalement sur les antidépresseurs, surtout les inhibiteurs sélectifs de la recapture de la sérotonine. Nous ne savons pas actuellement si les antidépresseurs sont efficaces chez les patients atteints à la fois de dépression et de démence. L’ECT (électroconvulsiothérapie) demeure un traitement adapté aux patients plus âgés déprimés qui ont cessé de s’alimenter ou de boire, qui ont des symptômes psychotiques ou qui présentent un comportement suicidaire. Associer un antidépresseur à une psychothérapie est recommandé bien que les preuves chez les sujets plus âgés soient limitées. De nouveaux traitements de stimulation cérébrale comme la stimulation magnétique transcrânienne sont actuellement testés chez des sujets plus âgés anxieux et dépressifs mais restent à l’état d’étude. Il semble possible de prévenir l’anxiété et la dépression chez les sujets plus âgés et un programme de soins par étapes a montré des résultats prometteurs.
Anxiety disorders and depression are highly prevalent, often chronic if untreated, and associated with severe suffering, functional disability, and reduced quality of life. Cognitive behavior therapy (CBT) has been shown to be an effective treatment, but is accessible to only a few. In the last decade, Internet-based CBT (ICBT)—self-help CBT with online therapist contact—has demonstrated promising results in the treatment of anxiety disorders and depression. The present paper presents an overview of the field of ICBT for anxiety disorders and depression. We define ICBT and provide a brief report on the state of the evidence, including cost-effectiveness. The main conclusion is that ICBT is an effective, well-documented and cost-effective treatment for anxiety disorders and depression. It is ready for implementation on a large scale.

Anxiety disorders and depression are highly prevalent psychiatric disorders affecting a majority of the adult population in Western countries at some point during the lifespan.1-3 For the affected individual, the consequences are severe, including functional disability, reduced quality of life, and risk of developing other psychiatric and somatic disorders.2-4,4-11 From a societal perspective, anxiety disorders and depression constitute a substantial economic burden for society in terms of, for example, sick leave, worsened somatic health, increased healthcare utilization, and risk of disability pension.9,12,14

During the last 45 years, cognitive behavior therapy (CBT) has gone from being a promising new treatment to the most well-established psychological treatment for anxiety disorders and depression.15 In several hundreds of randomized controlled trials (RCTs), CBT has been shown to be effective in treating these disorders16-17 and is a first-line treatment for these conditions. This is due to superior treatment effects in combination with high safety. In general, long-term follow-up studies indicate that improvements gained after CBT endure over several years (for example, see reference 18). In combination with relatively low intervention costs, CBT is thus a highly promising treatment from a societal cost-effectiveness perspective.

However, accessibility to CBT is limited. Lack of trained therapists and remote location of outpatient clinics in areas with low population density result in few being offered effective psychological treatment in rural areas.19 Thus, there has been a large need for developing treatments in which therapist time can be used more efficiently.
With the advent of the Internet, a new kind of treatment was made possible—Internet-based CBT (ICBT). Building on the well-documented effects of self-help treatment for anxiety, the general idea was to administer CBT in the form of self-help over the Internet with online therapist contact. The results from the first RCT in which ICBT was tested for headache showed that this treatment was feasible and efficacious, with promising effect sizes. Since then, the research on ICBT for anxiety disorders and depression has been performed at a remarkable pace. To date, more than 25 RCTs have been conducted by independent research groups on anxiety disorders and depression alone.

The aim of this paper is to provide an overview of ICBT for anxiety disorders and depression (primarily focusing on the work conducted in Sweden). More specifically, we describe what ICBT is, its applications, the role of the therapist, and the current state of the evidence, including health economic data. Finally, we discuss strengths and limitations of ICBT and potential future directions.

**Definition of ICBT**

Several forms of computerized CBT have been developed, making it difficult to speak of ICBT as one clearly defined treatment. These treatments have differed in several aspects, including technical solutions, degree of therapist contact, and diagnostic procedures. In the present paper, we focus on the model of ICBT that was originally developed in Sweden, which to date is the most well-researched paradigm. In Sweden, the research on ICBT was pioneered by Professors Gerhard Andersson and colleagues (Linköping University), Per Carlbring and colleagues (Umeå University), and for subsequent clinical implementation research, Professor Nils Lindefors and colleagues (Karolinska Institutet). Internationally, research groups in the Netherlands and Australia have also produced numerous studies on this format of ICBT. The general idea is that ICBT should reflect the content of conventional CBT, but is administered as a form of therapist-guided self-help delivered via the Internet. The ICBT treatment consists of modules or chapters, each corresponding to a session in conventional CBT, which the patients gain gradual access to as they progress through the treatment. The total amount of text is generally equivalent to 100-175 text pages. As CBT is disorder-specific, in terms of treatment and treatment models, the content of the modules varies across disorders.

Throughout the treatment, patients have regular contact with an online therapist that provides guidance in terms of feedback on homework exercises, advice on how to conduct the treatment, and answers to questions. The therapist also provides surveillance of the pace of treatment progress and grants patient access to the text modules. The therapist is highly trained in CBT, often a licensed psychologist, and has the same treatment responsibility as in conventional CBT.

The term “guided self-help” refers to the relatively limited therapist contact of ICBT as defined here. Often, the therapist spends 5-10 minutes weekly per patient, which is about 10%-20% of the time required by face-to-face CBT. This means that the patient carries a very large part of the responsibility, hence the term “self-help.” Therapist contact is provided online through a messaging system resembling e-mail. In general, there is no face-to-face or telephone contact between therapist and patient. Along with the module content and the therapist contact, ICBT often also entails online worksheets, which the patient can use to report daily activities of relevance for the treatment, such as thoughts and emotions in certain situations. The worksheets also provide an important information source for the therapist who can use these to follow the progress of the therapy.

As the content of the treatment is disorder-specific, the diagnostic procedure prior to treatment start is of great importance. In fact, as the structure of ICBT is much more static than face-to-face CBT, we view it as even more important that the patient is correctly diagnosed. That is, the psychologist does not have the same flexibility to compensate for misclassification and to adapt the content of the treatment once therapy has started. For a schematic of typical patient flow through a clinical ICBT process, see Figure 1 (page 348).

**Role of the therapist**

Several studies indicate that treatment outcome is improved when therapist contact is included in ICBT. For example, a meta-analysis by Palmqvist and coworkers showed that there was a strong correlation between amount of therapist time spent in studies of ICBT and the improvement demonstrated posttreatment. In addition, a meta-analysis by Spek and coworkers showed that ICBT studies that did not include any therapist contact produced markedly lower effect sizes (Cohen’s d=0.24) than studies that included therapist contact (d=1.00).

However, the role of the therapist is somewhat different compared with conventional CBT. As the only way of communication is through e-mail-like text messages summing up to around 5 to 10 minutes per week, the most important func-
tion of the therapist is to provide encouragement and to guide patients through the text material. In fact, 2 studies by Titov, Robinson, and coworkers, in which patients were randomly assigned to a skilled CBT therapist or to a technician without clinical experience, showed that participants in both treatment conditions made large and equivalent improvements. Moreover, although therapeutic alliance is considered to be an important factor in determining the outcome in face-to-face psychotherapy, a study of ICBT for posttraumatic stress disorder (PTSD) by Knaevelsrud and coworkers failed to show a meaningful relationship between treatment outcome and the early alliance between the patients and online therapists. Thus, it seems to be important to include therapist assistance in ICBT. However, judging from the evidence at hand it does not seem to be important that the therapist is highly skilled nor that a therapeutic alliance in the traditional sense is crucial for treatment success. We believe that the firm structure of ICBT makes the between-therapist variability in terms of therapeutic skills, treatment adherence, and even online-interpersonal skills less important than in traditional face-to-face CBT.

Despite these results, we still recommend that ICBT should always entail supervision by a clinical psychologist. This is because expertise is needed in complex cases and when patients significantly deteriorate during treatment, e.g. a sudden increase in suicidal ideation. In addition, developing and refining the treatment modules is a very important part of clinical ICBT work, and this cannot be carried out without in-depth knowledge in theory and practice of CBT.

**Applications**

- **Anxiety disorders**

ICBT treatment packages have been developed and tested for the large majority of anxiety disorders according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Specific disorders include social anxiety disorder, panic disorder, generalized anxiety disorder, PTSD, severe health anxiety (hypochondriasis), and obsessive-compulsive disorder. In addition, ICBT for anxiety disorders and depression has been tested within a transdiagnostic approach. In nearly all studies, ICBT has been administered to patients of at least 18 years of age. A few studies have investigated the effects of ICBT in children with disorders. In a recent meta-analytic review, Calear and coworkers found 2 studies using ICBT in the treatment of anxiety disorders and 1 study investigating ICBT for depression.

- **Depression**

One of the first disorders for which an ICBT treatment was developed was major depression. To our knowledge, all conducted RCTs aimed at treatment of depression have so far been carried out in mild-to-moderately depressed patients. Our own anecdotic clinical experiences support the possibility to use ICBT for severe depression as well. We have found no studies of ICBT for dysthymia or the bipolar disorders.

- **Other conditions**

It is important to underscore that Internet-delivered treatment programs have been developed and tested for a large number of disorders besides anxiety disorders and depression. These are irritable bowel syndrome, insomnia, chronic pain, bulimia nervosa, compulsive gambling, and obesity.

**Evidence of ICBT**

As stated above, the scientific evidence supporting ICBT has been increasing rapidly within the last decade. In a recently published meta-analysis of ICBT for anxiety disorders and depression, Andrews and coworkers report the findings of 22 RCTs of ICBT. For reference in interpreting the following estimates, an effect size >0.80 can be regarded as indicative of a large effect. For social anxiety disorder (8 RCTs), the overall effect size was 0.79 (g) with a number needed to treat (NNT) of 2.39. For panic disorder (6 RCTs), the average effect size was g=0.83 (NNT=2.26). For general anxiety disorder (2 RCTs), the average effect size was g=1.12 (NNT=1.75). For major depression (6 RCTs), the average effect size was g=0.78 (NNT=2.39). We have found 5 RCTs reporting the effects of ICBT for PTSD where effect sizes ranged from 0.47 to 1.39. As for severe health anxiety, only 1 RCT has been published so far. In that study, effect sizes on the primary outcome measure were between 1.94 and 2.09. In the field of obsessive-compulsive disorder, only 2 open trials have been published so far. In those studies, within-group effect sizes have ranged from 1.3 to 1.6.

![Figure 1. Patient flow through a typical clinical ICBT process. This example is tested in the Internet-based cognitive behavior therapy (ICBT) clinic in Sweden at the Psychiatric Clinic Southwest, Karolinska University Hospital (Huddinge).](image-url)
Taken together, the accumulated evidence clearly indicates that ICBT is an effective treatment for anxiety disorders and depression. This is underlined by the 5 RCTs that did not find any difference in treatment effect between face-to-face CBT and ICBT for social anxiety disorder\(^1\)\(^2\) and panic disorder.\(^3\)\(^4\)

**Health economy**

As ICBT requires a relatively limited amount of therapist time, it is a promising treatment from a cost-effectiveness perspective. Cost-effectiveness is often expressed in so-called incremental cost-effectiveness ratios (ICERs), which is a measure that combines the additional costs with the additional net benefits of a new treatment compared with an alternative.\(^5\)\(^6\)

In a cost-effectiveness study comparing ICBT with cognitive behavioral group therapy (CBGT) for social anxiety disorder, we found that ICBT was highly cost-effective as it yielded large effects and equivalent effect sizes compared with CBGT while being less costly.\(^5\)\(^7\) Taking a societal perspective, i.e., considering direct as well as indirect costs, we found that patients in both treatments had significantly reduced their costs at follow-up. However the ICER was $7046 indicating that for every additional improvement achieved when administering ICBT instead of CBGT (ICBT was slightly more effective), societal costs were reduced by more than $7000.\(^5\)\(^7\)

We have found the same encouraging results when investigating the cost-effectiveness of ICBT for irritable bowel syndrome.\(^5\)

**Strengths and limitations of ICBT**

We view the advent of ICBT for anxiety disorders and depression as highly important, as the strengths of ICBT are legion. First, ICBT is clearly effective, meaning that it significantly reduces anxiety and depressive symptoms. Second, ICBT requires little therapist time, which means that health care resources can be used more efficiently. Ultimately, this means that ICBT can be a way of increasing availability to CBT. Third, ICBT can bridge long distances between clinic and patient. Fourth, as the patient and therapist can work with the treatment at their own pace and at time points that are most suited for them, ICBT is very flexible and reduces the need for the patient to take time off from work. It also means that the phenomenon of cancelled appointments has been abolished in the health care context of ICBT. Fifth, ICBT seems to be cost-effective, meaning that ICBT could be a way of using limited health care resources in a way that enables greater accessibility to effective treatment.

As for limitations, there are relatively few in comparison with conventional CBT. However, there are some important drawbacks. These include the fact that one needs to have access to a computer and an Internet connection. One also needs to be able to read and write in the same language as the therapist. A third limitation, as stated above, is that it is even more essential than in conventional CBT to have a diagnostic procedure that is of high quality. If a patient suffers from PTSD, but is misclassified and receives treatment for social anxiety disorder, it is nearly impossible to adjust for this if the therapist detects the misclassification during treatment. Finally, from a therapist perspective, the reinforcement experienced from having truly helped a patient in conventional CBT can hardly be achieved in ICBT. This means that when administering ICBT, the health care provider needs to make sure that the therapist can be motivated by other forms of incentives. Our experience is that one such incentive that ICBT offers is a great possibility for integrating research into one's clinical work.

**Future directions**

There are several potential avenues for future research. One major path will most certainly be the expansion of ICBT to child psychiatry. We also predict that ICBT will be used in combination with other treatments. This could be within a stepped-care context or in simultaneous combination. A novel line of pharmacological treatment combination will be to add c-cycloserine\(^5\)\(^9\) to ICBT as a means to enhance the effect of ICBT. There is also room for much improvement of ICBT in combination with smartphone applications. Such applications could be used to remind the patient to register behaviors or to practice new skills learned in therapy.

Finally, perhaps the most important future direction is to make sure that ICBT is accessible to the many suffering from anxiety disorders and depression. We strongly believe that ICBT, within a time frame of 10 years, will be a standard feature of psychiatry in every industrialized country. Or at least we hope it will be.


44. Knaeveltrud C, Maercker A. Does the quality of the working alliance predict treatment outcome in online psychotherapy for traumatized patients? J Med Internet Res. 2006;8:e31.


Les troubles de l’anxiété et de la dépression ont une prévalence élevée, deviennent souvent chroniques s’ils ne sont pas traités et sont associés à une souffrance importante, à une incapacité fonctionnelle et à une qualité de vie diminuée. La TCC (thérapie cognitive comportementale) est un traitement efficace mais peu de personnes y ont accès. Ces 10 dernières années, une auto-TCC/TCCI (TCC par internet) à l’aide d’un contact en ligne avec un thérapeute, a montré des résultats prometteurs dans le traitement des troubles de l’anxiété et de la dépression. Cet article présente une vue d’ensemble de l’utilisation de la TCCI dans ces deux pathologies, en donne une définition et résume l’état des preuves ainsi que le rapport coût/efficacité. En conclusion, la TCCI est un traitement efficace, bien documenté et rentable de l’anxiété et de la dépression. Il est temps de procéder à sa mise en place à grande échelle.

Keywords: anxiety disorder; conventional cognitive behavior therapy; cost-effectiveness; depression; “guided self-help”; Internet-based cognitive behavior therapy
Far from being a pure mathematical quirk, fractals, and their iterative, pattern-within-pattern design, pervade our world. From coastlines to the shape of mountains, from clouds to lightning, from snowflakes to frost on your window, from ferns to broccoli, they are “Here, There, and Everywhere.” You breathe thanks to them, your blood flows thanks to them, they predict the vagaries of the stock exchange and even make your cellphone work. We are already beginning to be able to better treat our patients thanks to them. And they are BEAUTIFUL, they are the true music, poetry, fireworks of Creation! Learn more about fractals with two leading experts, who both were close friends with their discoverer, the French-American mathematician Benoit Mandelbrot.

The maverick mathematician: Benoît Mandelbrot and the stunning beauty of the fractal universe

N. Lesmoir-Gordon, UK

Fractals and their contribution to biology and medicine

G. A. Losa, Switzerland
The maverick mathematician: Benoît Mandelbrot and the stunning beauty of the fractal universe

by N. Lesmoir-Gordon, United Kingdom

Nigel Lesmoir-Gordon’s first book, Introducing Fractals, published in 2009, was translated in four languages and sold over 16,000 copies. It traced the roots of fractal geometry and the life of Benoît Mandelbrot, the maverick mathematician who set the stage for a revolutionary new discipline, fractal geometry. Nigel then went on to write, produce, and direct a highly successful documentary, The Colors of Infinity, on the discovery of the Mandelbrot set. This was followed by two broadcast documentaries: Is God a Number? which explores the mystery of consciousness and the power of mathematics in describing the universe; and Clouds Are Not Spheres—The Life and Work of the Maverick Mathematician, Benoît Mandelbrot. Nigel’s second book, based on his documentary, The Colors of Infinity, was published by Springer in 2010 and included contributions by leading experts in the field like Arthur C. Clarke, Professor Benoît Mandelbrot, Professor Michael Barnsley, Gary Flake, David Pennock, Will Rood, Professor Ian Stewart, and the Author. After the death of Benoît Mandelbrot on 14 October 2010, Nigel was invited to write obituaries for the Guardian and the Times. He also appeared on BBC Radio 4’s Last Word, discussing Mandelbrot’s life and work with Professor Ian Stewart of Warwick University.

Benoît Mandelbrot was born in Warsaw on 20th November 1924. When he was 12 and with the threat of war looming the family had the foresight to quit Poland and escape to France. He completed his education at the University of Paris with a PhD on Zipf’s law, after which he left France to take up residence in the USA. With his development of fractal geometry the visionary Benoît Mandelbrot has given science a new language to describe roughness and nature. Fractal geometry is an entirely innovative way to study and describe the real world. The discipline has opened up a host of new directions in science. Fractals seem intimately connected to the concepts of beauty and elegance. Amazingly, until recently there was no word to describe the familiar shapes of nature. Now we can see that there are fractals everywhere. Now we can view the universe through fractal eyes. On 1st March 1980 at IBM’s Thomas J. Watson Research Center in upstate New York, Benoît Mandelbrot discovered the now iconic Mandelbrot set. With its thrilling visualizations and infinite nature, it brought the world of mathematics back into public consciousness. And without fractals, your smartphone would be silent...

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On 1st March 1980 at IBM’s Thomas J. Watson Research Center in upstate New York Benoît Mandelbrot discovered the now iconic Mandelbrot set. With its thrilling visualizations and infinite nature it brought the world of mathematics back into public consciousness. British science fiction author, inventor, and futurist, Sir Arthur C. Clarke, famously known for his book and screenplay “A Space Odyssey,” and one of the “Big Three” alongside Isaac Asimov and Robert Heinlein, hailed the Mandelbrot set as “one of the most beautiful and remarkable discoveries in the entire history of mathematics, [...] one of the seven wonders of the world,” an opinion emphatically echoed by physicist John Archibald Wheeler, protégé of Niels Bohr and friend of Albert Einstein, quoted as saying: “No one will be considered scientifically literate tomorrow, who is not familiar with fractals.”

In my film The Colors of Infinity, which Clarke presents, he says: “No matter how much we magnified the Mandelbrot set, a million times, a billion times—until the original set was bigger than the entire Universe—we would still see new patterns, new images emerging, because the frontier of the Mandelbrot set is infinitely complex. And when I say infinitely, I really mean that. Most people when they say infinitely, they mean, ‘oh, only, rather big.’ But, this is really infinity!”

“The Mandelbrot set is one of the most beautiful and remarkable discoveries in the entire history of mathematics.” Sir Arthur C. Clarke. Image courtesy of Nigel Lesmoir-Gordon.
Fractal mountainscape. Photo Nigel Lesmoir-Gordon.

Fractal winter trees. Photo Nigel Lesmoir-Gordon.
Clouds are not spheres...
The seeds of this discovery were in fact sown decades before the Mandelbrot set was first seen. In Paris, in 1917, two French mathematicians, Gaston Julia, a student of Henri Poincaré, and Pierre Fatou, published papers connected with complex numbers. The results of their endeavors eventually became known as Julia sets. Although Julia and Fatou never saw a Julia set! They could only guess at them. And it would not be until the advent of modern computers that Julia sets could be seen for the first time. It was Mandelbrot’s uncle Szolem, who initially directed him to the work of Julia and Fatou.

The world that we live in is not naturally smooth-edged. The real world has been fashioned with rough edges. It’s a wiggly world! Smooth surfaces are the exception in nature. Throughout recent human history mankind has accepted a geometry that only describes shapes rarely—if ever—found in the real world. The geometry of Euclid describes ideal shapes—the sphere, the circle, the cube, the square. Now these shapes do occur in our lives, but they are man-made and not natural.

“Clouds are not spheres
Mountains are not cones
Coastlines are not circles
Bark is not smooth
Nor does lightning travel in a straight line”

Benoît Mandelbrot

Benoît Mandelbrot was a visionary, who has given science a new language to describe roughness and the way things really look, feel, and sound. Fractal geometry is an entirely new way to study and describe the natural world. The discipline has opened up a host of new directions in science.

Fractals are aesthetically pleasing, frequently revealing stunning beauty in the most subtle ways. The Mandelbrot set defies verbal description. Fractals seem intimately connected to the concepts of beauty and elegance. Amazingly until recently, there was no word to describe the familiar shapes of nature. Now we can see that there are fractals everywhere. Now we can view the universe through fractal eyes.

Benoît Mandelbrot’s early years in France and the first inkling of the fractals

Benoît Mandelbrot was born in Warsaw on 20th November 1924. Benoît showed an early delight in geometry. He excelled at chess, though he admits that he did not think the game through logically, but in a geometric fashion. When Benoît was 12, and with the threat of war looming, the family had the foresight to quit Poland and escape to France. When he turned 13 his uncle Szolem was appointed a professor of mathematics at the Collège de France in Paris, proving that a career in this subject was a real possibility. In 1937 Benoît attended the Lycée, but when Paris fell to the Nazis in 1940 the family fled further south to Tulle. Benoît went to Lyon for a year of post-high school study. It was here that he first discovered that he had a remarkable and extraordinary visual ability. He found that he could transform a mathematical problem into shapes.

After the liberation of France at the end of World War II Benoît returned to Paris to prepare for his examinations. Extraordinarily, he ended up passing the entrance exams without the usual two years of preparation!

Benoît started to study mathematics at the École Normale Supérieure, which trained university and high-school professors. But mathematics was dominated then by the Bourbaki group—a group of mainly French mathematicians founded in 1935—who wrote highly influential books on advanced mathematics based on set theory under the collective made-up pseudonym of Nicolas Bourbaki. (The group is still extant today, and true to its tradition, the names of current members are kept secret). Ironically Benoît’s uncle Szolem was one of the founders of the movement. The group sought to keep mathematics in the realm of the abstract and separate from real life. They based their ideas on the precepts of Plato. After just two days at The École Normale Supérieure something very significant happened to Benoît. He looked around and asked, “What am I doing here?” He spent a day agonizing and then resigned. This was a decision that set in train the path his life was to follow. He had been accepted into the most exclusive school, which would certainly have given him a guaranteed future. The alternative was to go to the École Polytechnique, which had a much less cohesive plan.

When he finished at the Polytechnique he moved to Caltech where he studied aeronautics, encountering the daunting complexity of turbulence. After Caltech Benoît went back to France to study at the University of Paris. He was a disappointed man “because the miracle of finding something special to do in America had not happened.”

He was looking for a PhD subject, which was not an easy task for Benoît! When visiting his uncle Szolem Benoît he asked him for something to read on the metro. Szolem reached into his waste-paper basket and pulled out a document. Benoît recalled him saying, “Somebody sent me this paper, which
is crazy, but you like crazy things. So here it is." Benoît took the paper with him. It was on Zipf’s law, which became the subject of his thesis. Once completed, he became a lecturer at the University of Lille and then went to the Massachusetts Institute of Technology to focus on information theory. After about six months at MIT he decided to move on to Princeton’s Institute for Advanced Study where he was sponsored by John von Neumann. Von Neumann introduced Benoît to the idea of the Hausdorff-Besicovitch dimension—the revelation that there were phenomena that existed outside one-dimensional space, but in somewhat less than two dimensions. Benoît adopted the Hausdorff-Besicovitch dimension on the spot. It was an almost ubiquitous tool and a special example of the wider concept of fractal dimension, which was to come.

**IBM and the price of cotton**

In 1958, he went to IBM as a faculty visitor for the summer. It was there that his ideas started to bear fruit and he decided to stay at IBM. The corporation gave Mandelbrot the funding, the facilities, a research team, and the mental space in which to work. The powers-that-be at IBM had vision, unlike the reactionary management of mainstream academia. It was a gamble, but it paid off. In just three years he had made his first major discovery.

Benoît was visiting Harvard to give a seminar in economics. His host had a drawing on the blackboard and Benoît asked, “How come you have the same drawing as I’ll be using in my lecture?” His host replied, “This drawing is on the behavior of cotton prices.” Benoît decided on the spot that cotton prices deserved extremely careful attention. When he got back to IBM he made a number of tests and those tests were successful. In a very short time he had a model for the variations of speculative prices. It was innovative and daring.

Economics, like most of the younger sciences, was attempting to imitate physics. In physics, the motion of a body must be continuous. It can’t just jump from one place to another, but economics can be very jagged and irregular and not continuous. In economics, Benoît argued, there’s no reason why prices should be continuous. If a piece of news arrives, a share price can go from, say, £100 to £10 or to £3. Benoît accepted the idea of discontinuity in his model of prices and strangely that idea had not occurred to anyone else.

**Carpets, gaskets, and sponges: a bizarre world of arcane mathematical objects**

Right at the beginning of Benoît’s career at IBM he tackled a practical issue, which directly involved and concerned his employers. Inside the company, data were being lost or corrupted when passing between computers by random noise bursts, which they could not get rid of or predict. He used the same tools he had learned as a student and which had been introduced into mathematics a hundred years before as
being so-called “pathologies.” Around 1900 objects like the Cantor set, the Sierpinski triangle, the Koch curve and the Menger sponge were known by a few, but they were mostly pure mathematicians, who were convinced that those objects or shapes proved that pure mathematical thought was quite separate from reality because they believed that those ideas had no practical implementation in nature. Benoît found that to be quite the contrary. Benoît grasped that the noise in the IBM system was deeply embedded in nature and impossible to drive out. He instantly doomed any attempts to predict, suppress, or eliminate it. This noise issue was an early and very clear example of the strange logic of fractals—the unruly collection of irregular geometric phenomena that only Benoît comprehended.

The Polish mathematician Vaclav Sierpinski introduced his fractal in 1916. The Sierpinski triangle or gasket is obtained by starting with a filled equilateral triangle, which is then divided into four smaller equilateral triangles, of which the middle one is removed, leaving a triangular hole. The three remaining filled equilateral triangles are then divided in exactly the same fashion, so that three smaller triangular holes appear. Conceptually, we can repeat this process indefinitely, at smaller and smaller scales, reaching, in the limit, Sierpinski’s gasket. The 3-dimensional version (illustrated here) constitutes a “Sierpinski pyramid.”

Georg Cantor’s quest for the meaning of continuity led him in 1883 to the set that is now named after him. It was one of the first fractals to be studied mathematically. The Cantor set: take a line and remove the middle third leaving two equal lines. Likewise remove the middle thirds from each of these two lines. Repeat this process an infinite number of times, and you are left with the Cantor set.

Austrian mathematician Karl Menger first described what became known as the Menger sponge in 1926. Menger was working in topology and was trying to develop a definition of dimension. It turns out that the sponge, which he created, is in fact a 3-dimensional fractal. The sponge has an infinite surface, but contains zero volume. All these shapes are incredibly complicated to describe in Euclidean terms, yet share an affinity with many shapes of modern mathematics, displaying an endless series of motifs within motifs repeated at all scales.

How long is the coast of Britain?
Acting like an 18th-century naturalist, Benoît scoured through forgotten and obscure journals in his quest for insight. Fortunately he uncovered the work of an eccentric and unremembered mathematician called Lewis Fry Richardson. Benoît had struck a rich seam and he knew it. The library at IBM was discarding books that nobody ever looked at. Fortunately

Richardson’s coastline paradox.
The length of the coast of Britain depends on the scale of measurement. In this scale model of Britain, ruler A measures 200 km; ruler B is 100 km, and ruler C is 50 km; at each measurement, the two ends of the ruler must touch the coast. The measurements found here are 2400, 2800, and 3450 km; empirical evidence shows that instead of reaching a finite number representing the true length of the coastline of Britain, the length of the coastline continues to increase and tends toward infinity as the length of the ruler gets smaller and tends toward 0. © Acadec/ Creative Commons.
Benoît was friendly with the librarian and she regularly told him when a truck was going to come and pick up discarded books. Benoît would look through them. Most of them were the proceedings of meetings that nobody was at all interested in and were only suitable for pulping. There was one periodical, however, which he opened more or less at random where he saw the name Lewis Fry Richardson. This name was already known to him through Richardson’s work on turbulence in the 1920s. Richardson was a great hero of Benoît. He was a very strange character. He was a very great man in many ways and was a true English eccentric.

What really struck Benoît were Richardson’s ideas on the lengths of coastlines. What appeared to be a simple question of geography exposed some of the essential features of fractal geometry. The closer you come, the longer the coastline becomes. And that’s where the idea of fractional dimension really came alive. Benoît found that his theory worked beautifully with coastlines. He produced a paper called “How Long is the Coast of Britain? — Statistical Self-Similarity and Fractional Dimension” (Science. 1967;156:636-638). In 1973 he started to develop an algorithm for creating real-looking coastlines.

He was preparing to publish his first book in France in 1975 and when the book was close to completion he knew he needed a name for his creation. One day he was thumbing through his son’s Latin dictionary, idly looking for a word he might adopt. He came across the word “fractus” which meant broken-up, fractional, irregular. He coined the word fractal. Though the idea of fractals in the form of iteration and self-similarity is an ancient one, it took this wanderer-by-choice to give the idea a name. Once named, the field took off.

**The Mandelbrot set**

On March 1st 1980 at IBM Benoît discovered what is now called the Mandelbrot set. The irony is that Mandelbrot’s uncle Szolem had strongly suggested that Benoît look at the papers which Julia and Fatou had published in 1917, with a view to making them the subject of his PhD. Reexamining the maths behind the Julia sets again in 1980 using a computer led Mandelbrot directly to the discovery of the Mandelbrot set.

During the First World War, Julia and Fatou had studied the rational mappings of the complex plane. They had also looked at the process of iteration. Although their work remained largely unknown to most mathematicians, we now know that this was because without modern computer graphics it was almost impossible to communicate their subtle ideas. Self-similarity was also well-known to Julia and Fatou. It would not be until the advent of modern computers though that Julia sets could be seen in their full glory.

Benoît: “For me, the first step with any difficult mathematical problem was to program it and see what it looked like. We started programming Julia sets of all kinds. It was extraordinary great fun! At one point we became particularly interested in the Julia set of the simplest possible transformation: z goes to z squared plus c, $f(z) = z^2 + c$.”

The Julia sets for this mapping depend only on the value of the parameter c. When c is small, they are simple loops, like wrinkled circles. For large values of c, the fractal consists of innumerable many discrete points, spread out and dust-like. When the first picture of the set rolled off the printer, Benoît and his colleagues’ first reaction was that there must be some mistake, a fault in the program perhaps. The picture was extremely strange and unexpected. Over a period of weeks, working late into the night in the basement of a laboratory in Harvard University, Benoît and his assistant explored the astonishing new world they had discovered. By feeding new coordinates into their program, they made successfully deeper zooms into the boundary of the set. One of the most striking discoveries was that buried deep within the seething froth of the object’s boundary, were tiny replicas, almost identical to the original set. Zooming further into these baby Mandelbrot sets they encountered further variations of these very same patterns with added frills and embellishments.

Benoît recalled: “We made many pictures of it. The first one was very rough. But the very rough pictures were not the answer. Each rough picture asked a question. So we made another picture, another picture. And after a few weeks we had...”
this very strong, overwhelming impression that this was a kind of big bear we had encountered!” Benoît and his team pushed the computers of the day to their extreme limits to refine their images. The beauty of the set, which revealed itself, was all the more extraordinary and exciting because it was totally unexpected.

There is an interesting parallel here with the equation that almost everybody is familiar with: \( E = mc^2 \). Albert Einstein’s equation, which states that matter and energy are equivalent to each other. That was a very simple equation, but with very far-reaching consequences. And the equation for the Mandelbrot set is equally simple \( z \leftrightarrow z^2 + c \). The letters in the Mandelbrot equation, though, stand for numbers, unlike those in Einstein’s equation where they stand for the physical quantities: mass, velocity, and energy. The Mandelbrot set equation numbers are coordinates, positions on the plane, defining the location of a spot. Another difference from Einstein’s equation—and a very important one—is the two-way arrow in the middle.

\[ z \leftrightarrow z^2 + c \]

It is a kind of two-way traffic sign. The numbers flow in both directions, constantly feeding back on themselves. This process of going round and round a loop is called iteration. It is rather like a dog chasing its own tail: the output of one operation becomes the input of the next and so on and so on. When the Mandelbrot equation is given a number representing a point and that number is iterated through the equation one of two things happens. Either the number gets bigger and bigger and runs out to infinity or it shrinks down to zero. Depending on which happens, the computer then knows where to draw a boundary line. So, what is obtained from this basic iteration is a map, dividing this world into two distinct territories. Outside it are all the numbers that have the freedom of infinity. Inside it, numbers that are prisoners, “trapped and doomed to ultimate extinction.”

No matter how much we magnify the set, a million times, a billion times until the original set is bigger than the entire Universe—we would still see new patterns, new images emerging because the frontier of the Mandelbrot set is infinitely complex. This set is the most famous fractal of all. It’s not easy to describe it visually. It looks like a man, a cat, a cactus, or a cockroach. It has little bits and pieces that remind us of most anything we can see out in the real world, particularly living things. There is indeed an infinite variety in the Mandelbrot set just as there is in the world of nature. We see shapes that remind us of elephant trunks, tentacles of octopi, sea horses, and compound insect eyes. There is certainly some connection between the Mandelbrot set and the way nature operates. The Mandelbrot set is one of the few discoveries of modern mathematics to be assimilated by society as a whole. It has appeared on mugs, T-shirts, record sleeves, and in pop videos, even in cinema and television commercials.

Clouds, Hokusai, and smartphone antennas

When Benoît was exploring this set he never felt that he had invented it. He never felt that his imagination was rich enough to invent all those extraordinary things. He knew he was making a discovery. “They were simply there, even though nobody had ever seen them before. It’s marvelous,” he said, “that such a very simple formula explains all these very complicated things! So the goal of science is starting with mess to explain...
by simple formulas. It’s the kind of dream of science. And in this case the dream was implemented in a fantastic fashion.” Though the stunning beauty of the images the Mandelbrot set generates appeal to us on many levels, the psychological reasons for this appeal are still a mystery. Perhaps there is some structure deep in the human mind that resonates to the patterns in the set. Like the Mandelbrot set, life is richest on the boundaries between land and sea. Between earth and sky. Consciousness and life itself exist at the edge of chaos. Nature often finds the same solution to many different problems. Like how to drain water from the land into the oceans, and how to get blood from our hearts to our fingertips and back again. And the templates that nature uses are fractals. Clouds look the same at all scales. It is impossible to determine the size of a cloud from a photograph of it. Clouds have now been shown to have the same dimension over 10 orders of magnitude, making them the most uniform fractal objects on the planet.

We may expect fractals to be found more often in nature, and Euclidean shapes more often in manufacture, but fractal designs have always appeared in architecture, whether for motives of utility, aesthetics, or the desire to mimic nature. They can be found in Islamic, Roman, Egyptian, Celtic, and Japanese paintings, in carpets and sculptures and in the work of Escher, Latham, and Hokusai. In the 1830s and 40s the Japanese artist Katsushika Hokusai produced marvelous woodblock prints, which clearly captured fractal aspects of nature. This woodblock “In the hollow of a wave off the coast of Kanagawa” from his Thirty-Six Views of Mount Fuji, is familiar to many.

Over his long life Hokusai observed that nature shows patterns that were then nameless, but which we now call self-similar, and these are frequently reflected in his work. Hokusai saw these patterns in nature and to us they certainly look like fractals related to the Mandelbrot set. Perhaps the resemblance to nature accounts for some of our pleasure in seeing mathematical fractals.

Benoît found his most enthusiastic acceptance first among applied scientists working with oil, rock, or metals. Fractals have become an organizing principle among physicists in the study of polymers and in the design of smartphone antennas. Earlier mobile phones had conspicuous antennas that had to be pulled out: now they are invisible, tightly packed inside your smartphone, folded according to a symmetrical and self-repetitive pattern at all scales, allowing their size to be shrunk up to 4 times and multiband and broadband functioning,
The stunning beauty of the fractal universe – Lesmoir-Gordon

Fractal design. © Bill Ross/Corbis.
without the need for multiple antennas. In addition, there is no need for additional components, as the fractal design creates a virtual combination of capacitors and inductors.

The way that a virus binds to a living molecule relies on the fractal structuring of both components. Fractal geometry is helping in the detection of cancerous cells in vitro and has provided the answer to the unusually long incubation period of the AIDS virus. Fractal growth methods are now used to model marine organisms such as sponges and coral. Scaling is also of interest in the study of vegetative ecosystems, earthquake data, and in the behavior of density-dependent populations.

Benoît was always willing to do things that others looked down on and dismissed. He had faith in his own insights and for many years it was not shared. But that did not daunt him. It was not easy to stick to it and to persist, but he always held fast to his vision and that vision has subsequently been wholly justified. Many people might have taken a glancing look at these things and when they did not yield or when others said it was nonsensical they might have gone on into other things. But not Benoît. He had vision and persistence and it is those qualities that made all the difference.

Fractal geometry is the language of nature, of the familiar and apparently random forms like trees, coastlines, rivers, lightning, the human body, a winding coastline, the branching structure of a fern, the spacing of stars in the night sky. With fractal geometry, the maverick Benoît Mandelbrot has given us a new language, which is applicable throughout all the sciences, and is one which has a mind-opening effect on most people who come across it. This new language is changing our lives and the world of scientific endeavor.
Fractal geometry “irrupted” into the life sciences during the “golden age” of cell biology between the 1960s and 1990s. Fractal dimension is a statistical measure that correlates the morphological structural complexity of cellular components and biological tissues. It measures qualitative morphological traits and self-similar properties. Most biological elements, whether at cellular, tissue, or organ level, have self-similar structures that can be characterized by means of the fractal dimension.

Fractals and their contribution to biology and medicine

by G. A. Losa, Switzerland

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The term Fractal coined by Mandelbrot from the Latin adjective fractus (fragmented, irregular) derives from the Latin verb frangere, meaning to break, to create irregular fragments. To be called fractals, biological and/or natural objects must fulfill a certain number of theoretic and methodological criteria including a high level of organization, shape irregularity, functional morphological and temporal auto-similarity, scale invariance, iterative pathways, and a noninteger peculiar fractal dimension [FD]. Whereas mathematical objects are deterministic invariant and self-similar over an unlimited range of scales, biological components and morphological structures are iterated entities statistically self-similar only within a fractal domain called “scaling window,” i.e., only within this scaling window can the scale-invariant (fractal) properties of an irregular object of finite size be observed. The latter needs to be experimentally established for each element, while the scaling range has to account for at least two orders of magnitude. The application of the fractal principle is very valuable for measuring dimensional properties and spatial parameters of irregular biological structures, for understanding the architectural/morphological organization of living tissues and organs, and for achieving an objective comparison among complex morphogenetic changes occurring through the development of physiological, pathologic, and neoplastic processes. Emphasis will be laid on the fractal contribution to the knowledge of cell membranes, hematological tumors, cell tissue cancers, and brain tissues in healthy and diseased states.

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T he Fractal Geometry of Nature, Benoît Mandelbrot’s masterpiece, has provided a novel epistemological framework for interpreting real life and the natural world in a way that avoids any subjective view.”1 Founded upon a body of well-defined laws and coherent principles, including those derived from chaos theory,2 fractal geometry allows the recognition and quantitative description of complex shapes, living forms, biologic tissues, and organized patterns of morphologic features correlated through a broad network of functional interactions and metabolic processes that shape adaptive responses and make the process of life possible. Obviously, this is in opposition to the ancient, conventional vision based on Euclidean geometry and widely adopted concepts, such as homeostasis, linearity, smoothness, and thermodynamic reversibility, which stems from a more intuitive—but artificially ideal—view of reality. In the chapter of his work entitled Epilog: The Path to Fractals, Benoît Mandelbrot wrote “The reader knows well that the probability distribution of fractals is hyperbolic, and that the study of fractals is rife with other power law relationships.” Although Mandelbrot’s famous seminal paper on statistical self-similarity and fractal dimension dates back to 1967,3 and the first coherent essay on fractal geometry was published 35 years ago,4 it is worth here recalling exactly how and when the “heuristic introduction” of this innovative discipline occurred or, more vividly expressed, when “the invasion of fractal geometry” into the life sciences such as biology and medicine actually took place.5

Although there no precise date can be given, it is generally agreed that fractal geometry was introduced during the “golden age” of cell biology—that is, between the 1960s and 1990s, under the impulse of Swiss and French groups.6,7 It was discovered that biologic elements, unlike deterministic mathematical structures, express statistical self-similar patterns and fractal properties within a defined interval of scales, termed “scaling window,” in which the relationship between the observation scale and the measured size or length of the object can be established and defined as the fractal dimension (FD).8 The fractal dimension of a biological component remains constant within the scaling window and serves to quantify variations in length, area, or volume with changes in the size of the measuring scale. However, concrete “fractality” exists only when the experimental scaling range encompasses at least two orders of magnitude, namely, spans two decades on the logarithmic scale axis. Data spanning several decades of scale have been previously reported in many other fields: thus, defining a “scaling range” appears an inescapable requisite for assessing the fractality of every biological element. This emphasizes Mandelbrot’s statement “fractals are not a panacea; they are not everywhere.”9

To conclude, the fractal dimension is a statistical measure that correlates the morphological structural complexity of cellular components and biological tissues.10 Fractal dimension is also a numerical descriptor that measures qualitative morphological traits and self-similar properties of biological elements. Recourse to the principles of fractal geometry has revealed that most biological elements, whether at cellular, tissue, or organ level, have self-similar structures within a defined scaling domain that can be characterized by means of the fractal dimension.

Cell membranes and organelles

Application of fractal geometry to cell biology stemmed from the discovery that cellular membrane systems had fractal properties. What started it all was the uncertainty of observations regarding the extent of cell membranes in the liver, as findings from morphometry studies of liver cell membranes by various laboratories failed to match. This triggered much debate as to which of these estimates was correct, and whether liver cells contained 6 or 11 m² of membranes per cm², quite a significant difference. This cast doubt on the reliability of stereological methods, since they yielded conflicting results when measurements were made under different magnifications of the electron microscope. Ultimately, it was found that the estimates of surface density of liver cell membranes increased with increased resolution.6 Mandelbrot suggested that these results were attributable to a scaling effect, analogous to the “Coast of Britain effect.”10 This explained why measurements of liver cell membranes at higher magnification yielded higher values than at lower magnification.6,11 This scaling effect applies mainly to cellular membranes with a folded surface or an indented profile, such as the inner mitochondrial membrane or the rough endoplasmic reticulum (ER). In fact, the surface density estimate of rough membranes was found to be increased with increasing magnification, while the surface density measure of the smooth outer mitochondrial membrane and of the smooth ER counterpart was only slightly affected by the resolution effect (Figure 1).6

Fractal analysis proved particularly useful with regard to electron microscopy for the objective investigation of fine cytoplasmic structures and the organization of various types of chromatin, nuclear components, and other subcellular organelles, both in normal and pathological tissues and cell cultures. Thus, external nuclear membranes (ENM) and nuclear membrane-bound heterochromatin (NMBHC) domains of human breast cancer MCF-7 cells briefly triggered by steroid hormones, such as 17β-estradiol or dexamethasone, were shown to undergo ultrastructural changes at the beginning of growth, which were quantified by their fractal dimensions. Indeed, after a very short treatment (5 min) with 17β-estradiol (1 nM), the ultrastructural irregularity or the DNA unfolding of the NMBHC domain was significantly enhanced as documented by an increase its fractal dimension, whereas with dexamethasone (1 nM) it was reduced. Neither steroid significantly modified the ENM ultrastructure. 

This fractal tool has also been employed to document the feasibility of using ultrastructural changes in cell surface and nuclear interchromatin to assess the early phases of apoptosis (programmed cell death) induced in human breast cancer SKBR-3 cells by the ionophore calcimycin. The ultrastructural changes that involved a loss in heterochromatin irregularity due to its increased condensation quantified by a lower fractal dimension were evident well before the detection of conventional cell markers, which were only measurable during the active phases of apoptosis. Similarly, it was shown that the nuclear complexity of human healthy lymphocytes underwent reduction during the apoptotic process. Measuring the fractal dimension of euchromatin and heterochromatin nuclear domains helped discriminate lymphoid cells found in mycosis fungoides from those in chronic dermatitis.

In histology and cytology, fractal morphometry applied to microscopic examination of cell nuclei and nuclear components has greatly improved the understanding of cell behavior and the diagnosis and prognosis of various disease states. Quantification of nuclear chromatin organization by fractal morphometry is used to evaluate the degree of malignancy in human breast cytology and in aspiration cytology smears of cervical lesions. Recent studies targeting the periphery of cell nuclei have shown fractal properties, making it possible to classify early ovarian cancers and even to distinguish normal from malignant liver cells.

Leukemia and hematological malignancies

Application of fractal morphometry to nonsolid cancers came later, when human leukemia cells of lymphoid and/or myeloid origin were characterized on electron microscopic images through quantitative measurement of membrane surface properties that could be correlated with specific phenotype markers. Cells isolated ex vivo from the blood of humans with acute T-lymphoid leukemia revealed pericellular membranes with a nearly smooth outline as documented by fractal dimension values significantly lower than those found for pericellular membranes of healthy blood cells. Healthy lymphocytes of B-cell lineage had a fractal dimension FD (1.20) significantly different from that of lymphocytes of T-cell lineage, ie, CD4-T helper (1.17) and CD8-T suppressor (1.23) cells (Figure 2). Unexpectedly, strongly proliferating T-lymphoid leukemic cells were found to possess a plasma membrane characterized by a low FD value (1.10), close to the FD value measured on the plasma membrane of in vitro growing lymphoblasts derived from mature T-lymphocytes triggered by phytohemagglutinin (PHA), a mitogenic lectin. About 80% of acute leukemia subtypes of the B-cell lineage (c-ALL and pre-B undifferentiated phenotype) showed plasma membranes with FDs ranging from 1.12 to 1.17, below the FD of the plasma membrane of differentiated B-lymphocytes. The remaining cases (20%) of acute lymphoblastic B-leukemia showed a more convoluted cell surface with FD values of up to 1.24. Cells from hairy-cell leukemia, a chronic type of human leukemia, with a highly convoluted plasma membrane morphology and a completely diff...
different surface phenotype displayed the highest FD, between 1.32-1.36.24 The fractal dimension of scale-invariant self-similar chromatin was measured in nuclei of blasts isolated from patients suffering from acute leukemia of the precursor B lymphoblastic type (B-ALL). The increase in FD, together with the accentuated coarseness of the nuclear surface, reflects significant changes in the DNA methylation pattern usually localized in heterochromatin nuclear regions and therefore was regarded as a bad prognostic factor for these patients.25

The usefulness of fractal analysis to assess the hematological cell phenotype and to define a clinical group was confirmed 20 years later by Mashiah et al.26 These authors used conventional slide preparations to analyze “nuclei contours” of cells belonging to the B lineage, ie, normal and reactive lymphocytes and lymphoid cells isolated from patients with chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL). They found that the fractal dimensions of perinuclear membranes were significantly different between the groups and all correlated with their biological properties, ie, that reactive lymphocytes (FD=1.20) were situated between CLL (FD=1.25) and normal cells (FD=1.13), while aggressive lymphoma cells had a significantly higher fractal dimension ranging from 1.23 (FL) to 1.31 (DLBCL). By comparing data from the latter papers dealing with hematological malignancies, it turned out that cells isolated from patients with different types of leukemia and/or lymphoma have nuclear chromatin with roughness or complexity (high FD value) increasing with increasing degrees of aggressiveness and malignancy, whereas pericellular membranes acted inversely and looked smoother (low FD value) in cells having a high degree of malignancy. One could infer that hematological tumors did not undergo uniform neoplastic transformations, but rather manifest a great number of metabolic and phenotype changes that imply either an increasing or a decreasing complexity of the morphological surface and an altered organization of cell components mainly dependent upon the cytotype under investigation. This contrasts with the behavior of several cell colonies of breast cancer origin and experimental tumors, which were observed to obey the same dynamics of proliferation and growth and display contours with self-similar fractal features when submitted to scaling analysis.27

Cancer tissues
For an objective description of neoplastic and pathologic traits of cell tissues by the fractal approach, a main condition is the experimental definition of a scaling interval rather than a unique dimensional scale selected a priori. A critical reading of the literature shows that such a distinctive characteristic is insufficiently taken into account and inadequately applied in many investigations, as exemplified by Baish and Jain:

These views are typically interpreted in a qualitative manner by clinicians trained to classify abnormal features such as structural irregularities or high indices of mitosis. A more quantitative and hopefully more reproducible approach, which may serve as a useful adjunct to trained observers, is to analyze images with computational tools. Herein lies the potential of fractal analysis as a morphometric measure of the irregular structures typical of tumor growth.28

Among the most promising fields of investigation, for which fractal geometry provides an original approach and fractal dimension represents more than an additional geometrical parameter or just “a useful adjunct,”29 are cell heterogeneity; architectural organization of tissues tumor; parenchymal border; cellular/nuclear morphology; and developmental and morphogenetic processes in tissues and organs in healthy, pathologic, or tumor conditions, and the pathologies of the vascular architecture. Tumor grading on histology specimens (a measure of the degree of cellular differentiation) is difficult to assess because tumors often consist of a heterogeneous mixture of cells with varying degrees of irregularity as well as local variations in cellular differentiation.

Measuring the fractal dimension could aid pathologists in grading heterogeneity and in determining the spatial extent of poorly differentiated regions of breast and prostate tumors.29 Cell heterogeneity, known to contribute in a determinant way to the histological grading of human breast cancer, has been examined by means of geostatistics and the Hurst fractal parameter.30 Several examples seem to indicate that the occurrence of morphogenetic dynamics, the emergence of complex patterns, and the architectural organization of active tissues and tumor masses may be driven by constructive mechanisms related to fractal principles, including deterministic and/or random iteration of constituent units with varying degrees of self-similarity, scaling properties, and form conservation.31 Preservation of tissue architecture and cell polarity of organs and the eventual restoration of organized traits in tumor tissues, deconstructed and deregulated at various levels, is an emerging field of interest since it has been observed that biological entities organize with their own degrees of structural and behavioral complexity and develop on different spatial and time scales.32-35 Stromal tissue has a major role in the control and regulation of physiological processes, in modulating tumorigenesis36-38 and eventually in inducing cancers to revert to normal tissues.39

Fractal dimension has been used as a characterization parameter of premalignant and malignant epithelial lesions of the floor of the mouth in humans40 and of architectural changes of the epithelial connective tissue interface (ECTI) of the buccal mucosa during aging (Figure 3).41

The outline roughness and the internal irregularity of collagen extracellular matrix examined on biopsy specimens of chronic liver diseases were evaluated by the fractal approach, which yielded a reliable measure much useful in describing these two qualitative properties of the liver matrix.42
Fractal morphology has provided quantitative information concerning the link between molecular, cellular, and tissue changes during the development of canine tumors (Figure 4).43 The onset of fundamental phenomena such as development, growth, and cell death during different stages of carcinogenesis and cell differentiation, ie, from mesenchymal to smooth muscle cells, has been adequately investigated by fractal geometry as recently reported.44,45 One highly promising approach appears to be a combination of fractal analysis, to provide a quantitative description of shapes, with radiographic imaging, which has the ability to discriminate malignant from benign tumor masses, as well as from normal tissue structures.46 The computed FD of the contour of a mass may be useful for characterizing shape and gray-scale complexity, which may vary between benign masses and malignant tumors in mammograms (Figure 5).47

<table>
<thead>
<tr>
<th>Age range</th>
<th>Mean box fractal dimension</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>1.1069 ± 0.03267</td>
<td>2</td>
</tr>
<tr>
<td>11-20</td>
<td>1.1117 ± 0.08987</td>
<td>2</td>
</tr>
<tr>
<td>21-30</td>
<td>1.1414 ± 0.07095</td>
<td>4</td>
</tr>
<tr>
<td>31-40</td>
<td>1.1290 ± 0.03822</td>
<td>4</td>
</tr>
<tr>
<td>41-50</td>
<td>1.0933 ± 0.05661</td>
<td>5</td>
</tr>
<tr>
<td>51-60</td>
<td>1.1373 ± 0.05657</td>
<td>8</td>
</tr>
<tr>
<td>61-70</td>
<td>1.0992 ± 0.04456</td>
<td>9</td>
</tr>
<tr>
<td>71-80</td>
<td>1.1260 ± 0.04751</td>
<td>5</td>
</tr>
<tr>
<td>81-90</td>
<td>1.0903 ± 0.01675</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 4. Microscopic view of canine ribbon type trichoblastoma of medusoid pattern with an irregular contour. Magnification 40×.


Fractals and their contribution to biology and medicine – Losa

Figure 5. Fractal analysis of contours of breast masses in mammograms. Thirty-seven benign breast masses and 20 malignant tumors were ranked by their fractal dimension FD estimated by the 1-D ruler method. B: benign, M: malignant.

Fractal theory has provided the basis for a unique software platform program, which has been developed for use in conjunction with magnetic resonance imaging (MRI), and has shown great promise in the early diagnosis and treatment of breast cancer. In a recent study where this advanced method was applied, more than 30% of the patients were shown to have additional tumors in the same breast, and in almost 10% of cases tumors were shown also to be present in the other breast. Image analysis combined with fractal analysis has been applied to describe changes in the actin cytoskeleton of neonatal cardiac fibroblasts responding to mechanical stress.


Brain, brain diseases, and neural tissue

The evolutionary concourse of two major events, “the tremendous expansion and the differentiation of the neocortex,” as reported by De Felipe, has contributed to the development of the human brain (Figure 6). Today, modern neurosciences recognize the presence of fractal properties in brain at various levels, i.e., anatomical, functional, pathological, molecular, and epigenetic, but not so long ago there was no analytical method able to objectively describe the complexity of biological systems such as the brain. The intricacy of mammalian brain folds led Mandelbrot to argue that “A quantitative study of such folding is beyond standard geometry, but fits beautifully in fractal geometry.” At that time however, there was no certainty about the brain’s geometry or about neuron branching. Anatomical-histological evidence that the complexity of the plane-filling maze formed from dendrites of neural Purkinje cells of cerebellum was more reduced in nonmammalian species than in mammals led Mandelbrot to comment: “It would be very nice if this corresponded to a decrease in D (fractal dimension), but the notion that neurons are fractals remains conjectural.” Since then, a wealth of investigations have documented the fractal organization of the brain and nervous tissue system, and the implication of fractals for neurosciences has been unambiguously affirmed. The brain consists of distinct anatomical areas formed by nervous tissue mainly composed of neurons and glial cells of distinct types. Neurons contain the axon (a long cytoplasmatic process associated with the cell body that communicates with target organs), and the dendrites (shorter cytoplasmatic processes off the cell body that allow communication between neurons), while glial cells of various types have a structural role as a net via their branched and unbranched protoplasmic processes (Figure 7). These anatomical, morphological, and physiological properties combine to create the brain’s complexity, which can only be modeled by a supercomputer. The growth and morphological differentiation of spinal cord neurons in culture and the degree of dendritic branching of thalamic and retinal neurons were among the first applications of fractal analysis. Further studies have confirmed that the fractal dimension correlates with the increase in morphological complexity and neuronal maturity (Figure 8). Fractal analysis was applied to anatomical/histological images and high-resolution magnetic resonance images in order to quantify the developmental complexity of the human cerebral cortex, the alterations in diseased brain with epilepsy, schizophrenia, stroke, multiple sclerosis, cerebellar degeneration, and the morphological differentiation of the peripheral nervous system. In the normal human retina, blood vessels or vascular trees exhibited an FD of 1.7, the same fractal dimension found for a diffusion-limited growth process, a finding that may have impli-
cations for the understanding of the embryological development of the retinal vascular system. Lastly, it has been shown that the quantitative evaluation of the surface fractal dimension may allow not only to measure the complex geometrical architecture, but also to model the development and growth of tumor neovascular systems and explore the morphological variability of vasculatures in nature, in particular the microvasculature of normal and adenomatous pituitary tissue.

Conclusions
Irregularity and self-similarity under scale changes are the main attributes of the morphological complexity of cells and tissues, both normal and pathologic. In other words, the shape of a self-similar object does not change when scales of measurement change because any part of it might be similar to the original object. Size and geometric parameters of an irregular object, however, differ when inspected at increasing resolu-

Figure 7. Fractal analysis of the three main types of human astrocytes. Grouped on columns are the original high-resolution images, the binary silhouettes and the outline masks together with the corresponding fractal dimension (FD) values. After reference 53: Pirici D et al. Rom J Morphol Embryol. 2009;50(3):381-390. © 2009, Romanian Academy Publishing House.

Figure 8. Application of the box-counting method to a dendritic branching pattern. A. The whole image is covered with a set of squares and squares that cover dendrites are counted. B. Log-log plot between number of squares (N) and square size (r) is fitted by a straight line. Fractal dimension $FD = 1.415$. $R$ is the correlation coefficient. After reference 57: Milosevic NT and others. J Theor Biol. 2008;259:142-150. © 2009, Elsevier.
Fractal Methodology

According to Mandelbrot “A fractal set is a set in metric space for which the Hausdorff-Besicovitch dimension D is greater than the topological dimension DT.” In nature, a fractal object is defined by its structural properties, namely, by surface rugosity and irregularity or absence of smoothness, form invariance or self-similarity, and complexity. The Richardson-Mandelbrot equation provides the mathematical basis for understanding geometric and spatial fractal structures, and for measuring and interpreting them, namely:

$$L(\varepsilon) = N(\varepsilon) \cdot \varepsilon^D$$ (1)

where $L(\varepsilon)$ represents the contour length (e.g., the perimeter) of the biological component under investigation, $\varepsilon$ the unit length of measure, and $N(\varepsilon)$ the number of unit lengths $\varepsilon$ needed to cover the contour $L(\varepsilon)$. By substituting $N(\varepsilon)$ with $[\log(1/\varepsilon)]$ into (1), the above equation can be transformed by logarithmic procedure and rewritten as:

$$\log[L(\varepsilon)/lo] = (1-D) \log[\varepsilon/lo]$$ (2)

which is the equation of a straight line with slope $1-D$, from which the dimensional exponent $D$ can be calculated to yield the numerical value of the fractal dimension $FD$.

As mentioned in the Introduction, biological fractals, also called asymptotic natural fractals, show autosimilar scaling properties (fractality) within a fractal window, graphically represented by the region II in the middle of three typical regions, limited by a lower ($\varepsilon_{\min}$) and an upper bound ($\varepsilon_{\max}$), of an asymptotic fractal, where a straight line can be drawn and the fractal dimension $[FD]$ calculated from its slope (Figure). While the practical evaluation of the fractal dimension could be obtained by various quantitative approaches, the box counting method easily based on counting of the nonempty boxes $N$ at a variable grid length ($\varepsilon$), is by far the most reliable.

The three typical regions of an asymptotic fractal.

Asymptotic natural or biological fractals only show autosimilar scaling properties (fractality) within a fractal window, represented by the region II, limited by a lower ($\varepsilon_{\min}$) and an upper bound ($\varepsilon_{\max}$) (dashed lines), where a straight line can be drawn and the fractal dimension [FD] calculated from its slope, using the logarithmic relation $D = \log N(\varepsilon)/\log(1/\varepsilon)$.


Fuseler JW, Milette CF, Davis JM, Carter W. Fractal and image analysis of morphologic changes in the actin cytoskeleton of neonatal cardiac fibroblasts in response to mechanical stretch. Microsc Microanal. 2007;13:133-143.


Biophys J. 2003;85:2948-2961.


Keywords: brain; brain disease; form invariance; fractal dimension [FD]; fractal geometry; irregular morphology; leukemia; nervous tissue; non-Euclidean dimension; scaling window; self-similarity; solid tumor

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**Les fractales et leur contribution à la biologie et à la médecine**
