ISSN 1294-8322

Dialogues in clinical neurosciences

Anxiety I

2002 Volume 4 · No. 3

Dialogues
in clinical neuroscience

Editorial

Dear Colleagues,

Anxiety results from the stimulation of innate brain systems that respond to possibly threatening changes in our world. Thus, anxiety is linked to the cognitive evaluation of both internal physiological variables and external parameters in the environment. At the simplest level of organization, anxiety's manifestation is the flight response in the lower forms of organism. In more evolved species, the emotional component of anxiety becomes more visible and modulates behavior that is less genetically determined. In humans, the psychoanalytic approach greatly modified the symptomatic description of anxiety disorders, which were subsequently conceptualized as neuroses. Our knowledge of anxiety has undergone a new revolution in recent decades, with the discovery of new pharmacological and psychotherapeutic approaches.

This is the first of two issues of *Dialogues in Clinical Neuroscience* devoted to anxiety. A series of neuroscience and clinical articles will attempt to shed some light on various aspects of anxiety, such as its biological basis, the role of genes, the validity of human models, and the current state of neuropsychopharmacology in this indication. Numerous other questions will probably come to the reader's mind. We want to express our appreciation to the authors who contributed to this issue for the challenging thoughts they offer to the readers of *Dialogues in Clinical Neuroscience*.

Yours sincerely,

Jean-Paul Macher, MD

Marc-Antoine Crocq, MD

Dialogues in Clinical Neuroscience is a quarterly publication that aims to serve as an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects. Each issue addresses a specific topic, and also publishes free contributions in the field of neuroscience as well as other non–topic-related material.

PUBLISHER

Les Laboratoires Servier
22 rue Garnier - 92200 Neuilly-sur-Seine - France
E-mail: mail.dialneuro@fr.netgrs.com

ISSN 1294-8322

Design: Christophe Caretti / Layout: Graphie 66
Imprimé en France par SIP
1, rue Saint Simon - 95310 Saint-Ouen-l'Aumône

Contents

Page

ISSUE COORDINATED BY: *Pierre SCHULZ*

Contributors

Thierry Steimer, PhD

Author affiliations: Clinical Psychopharmacology Unit, Geneva University Hospital, Chêne-Bourg, Switzerland

Deborah J. Morris-Rosendahl, PhD

Author affiliations: Institute for Human Genetics and Anthropology, Albert Ludwigs University of Freiburg, Germany

Hanns Möhler, PhD

Author affiliations: Institute of Pharmacology and Toxicology, University of Zurich, Department of Applied Biosciences, and Federal Institute of Technology (ETH) Zurich, Switzerland

Giovanni B. Cassano, MD

Author affiliations: Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnology, University of Pisa, Italy

Jerome Kagan, PhD

Author affiliations: Department of Psychology, Harvard University, Cambridge, Mass, USA

Donald F. Klein, MD

Author affiliations: Columbia University, New York State Psychiatric Institute, Department of Therapeutics, New York, NY, USA

Jean Cottraux, MD, PhD

Author affiliations: Anxiety Disorder Unit, Hôpital Neurologique, Lyon, France

In this issue...

The ***State of the art*** article in this issue is about the biology of fear and other emotions that relate to anxiety. Thierry Steimer (page 231) quotes authors from 19th and 20th centuries who underlined the three aspects of emotions: physiology, subjective feelings, and behavioral changes. He then integrates these manifestations of emotions with structural and functional aspects of the central nervous system. The challenging message is that there exists rather specific central nervous system circuitry for each emotion, or even for each aspect of a given emotion.

The field of genetic studies in psychiatry is steadily expanding. Deborah J. Morris-Rosendahl has written a ***Basic research*** review (page 251) to present what is known about the genetics of anxiety disorders, in particular the complex genetics of nonmendelian phenotypes. For most traits and disorders, a large number of different genes might be involved. However, there are already fascinating data showing that single-gene polymorphisms explain part of the variance in the epidemiology of anxiety disorders. Not surprisingly, genes related to enzymes or receptors of the monoaminergic systems have been implicated. This review also lists a series of unexpected results, for example, those tied to the fascinating relationship between joint hypermobility and phobias.

The GABAergic (GABA, γ-aminobutyric acid) system is known to be a major inhibitory neurotransmittor system and is the target of antianxiety medication, for example, benzodiazepines. This system could also be involved in the pathophysiology of anxiety disorders. Molecular techniques that manipulate the structure and functioning of the subunits of the $GABA_A$ receptor confirm that specific differences in receptors can have far-reaching behavioral consequences. In his ***Basic research*** article (page 261), H. Möhler presents an update of the pharmacology of the neuronal inhibition by benzodiazepines, discussing the major clinical effects of these compounds in relation to spontaneous or induced changes in GABAergic receptors. He also discusses the clinical relevance of the GABAergic system for major psychiatric disorders.

The ***Pharmacological aspects*** of anxiety disorders were reviewed by Giovanni B. Cassano, Nicolò Baldini, and Stefano Pini (page 271), who state that there is no ideal anxiolytic. They review the issue of efficacy in terms of response versus remission, the risk of dependence, and the symptoms of withdrawal for several categories of medication. It is interesting to note that a number of anxiolytic compounds belong to other pharmacological categories, such as antidepressants or β-blocking drugs. The results with each category of medication are described by the authors under each major anxiety disorder diagnosis, making this article highly useful for taking evidence-based decisions in the pharmacological treatment of anxiety disorders.

In his ***Clinical research*** article (page 287), Jerome Kagan reviews the results of the long-term studies that he set up with his collaborators to assess childhood predictors of states of anxiety. He has studied children from the age of 4 months onwards, and has shown that physiological variables as well as behavioral variables are stable over time and that they have a predictive value of the evolution of the child at the age of 11. Children considered as shy or inhibited at an early age seem to have a higher risk of anxiety disorders, in particular social phobia. These fascinating results are a bridge between temperaments and axis I *DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)* disorders. The concept of heterotypic continuation means that a given characteristic expresses itself differently according to the age of the subject, a concept well illustrated by the work of Kagan and his collaborators.

Donald F. Klein has played a major role in the identification of panic disorder. Indeed, he was the first to report that imipramine was useful for the treatment of these patients. He has contributed much to a better definition of anxiety states, their treatment, and their pathophysiology. In this ***Clinical research*** review (page 295), he gives us his view of the evolution of the concept of anxiety during the last 100 years. The reader is offered a fascinating overview, ranging from historical and early clinical observations to recent pathophysiological hypotheses concerning the mechanisms of panic attacks. This overview is a tribute to both astute clinicians and the recent development of major efforts in biological psychiatry research.

In the ***Clinical research*** section (page 305), Jean Cottraux reviews the efficacy of cognitive behavior therapy (CBT) in anxiety disorders such as panic disorder, generalized anxiety, posttraumatic stress disorder, and phobia. The efficacy of CTB is comparable to that of pharmacological treatment. This review confirms the generally held opinion that other psychotherapeutic techniques such as psy-

In this issue...

chodynamic therapy, psychoanalysis, and relaxation techniques have not been studied as often as CBT, and that these techniques have a lesser efficacy in anxiety disorders. The issue of the possibly deleterious effects of a single session of debriefing for the prevention of post-traumatic stress disorder is rightly mentioned. What we learn from studies in which medication and different forms of psychotherapies were combined is that combination therapy is as efficacious—or even more efficacious—than monotherapy, and with no antagonistic effect.

Pierre Schulz, MD

Erratum

The photograph of the author of the article by Johannes M. H. M. Reul and Florian Holsboer (On the role of corticotropin-releasing hormone receptors in anxiety and depression. *Dialogues Clin Neurosci*. 2002;4:31-46), which appeared on the *Contributors* page of the issue on *Pathophysiology of Depression and New Treatments*, was a photograph of Johannes M. H. M. Reul, and not Florian Holsboer, as indicated.

We apologize for any inconvenience this may have caused.

The biology of fear- and anxiety-related behaviors

Thierry Steimer, PhD

Anxiety is a psychological, physiological, and behavioral state induced in animals and humans by a threat to well-being or survival, either actual or potential. It is characterized by increased arousal, expectancy, autonomic and neuroendocrine activation, and specific behavior patterns. The function of these changes is to facilitate coping with an adverse or unexpected situation. Pathological anxiety interferes with the ability to cope successfully with life challenges. Vulnerability to psychopathology appears to be a consequence of predisposing factors (or traits), which result from numerous gene–environment interactions during development (particularly during the perinatal period) and experience (life events). In this review, the biology of fear and anxiety will be examined from systemic (brain–behavior relationships, neuronal circuitry, and functional neuroanatomy) and cellular/molecular (neurotransmitters, hormones, and other biochemical factors) points of view, with particular reference to animal models. These models have been instrumental in establishing the biological correlates of fear and anxiety, although the recent development of noninvasive investigation methods in humans, such as the various neuroimaging techniques, certainly opens new avenues of research in this field. Our current knowledge of the biological bases of fear and anxiety is already impressive, and further progress toward models or theories integrating contributions from the medical, biological, and psychological sciences can be expected.

Dialogues Clin Neurosci. 2002;4:231-249.

In a book published in 1878 (*Physiologie des passions*), Charles Letourneau, who was contemporary with the French neuroanatomist Paul Broca, defined emotions as "passions of a short duration" and described a number of physiological signs and behavioral responses associated with strong emotions.[1] Emotions are "intimately linked with organic life," he said, and either result in an "abnormal excitation of the nervous network," which induces changes in heart rate and secretions, or interrupt "the normal relationship between the peripheral nervous system and the brain." Cerebral activity is focused on the source of the emotion; voluntary muscles may become paralyzed and sensory perceptions may be altered, including the feeling of physical pain. This first phase of the emotional response is followed by a reactive phase, where muscles come back into action, but the attention still remains highly focused on the emotional situation. With the knowledge of brain physiology and anatomy that was available at the end of the 19th century, hypotheses on the mechanisms possibly involved in emotions were of course limited. However, Letourneau assumed that "the strong cerebral excitation" that accompanies emotions probably only concerned "certain groups of conscious cells" in the brain and "must necessitate a considerable increase of blood flow in the cell regions involved."[1] He also mentioned that the intensity, the expression, and the pathological consequences of emotions were directly linked to "temperaments" (which he defined within the four classic Hippocratic categories).

Keywords: *anxiety; fear; emotions; animal models; neurobiology; behavior*

Author affiliations: Clinical Psychopharmacology Unit, Geneva University Hospital, Chêne-Bourg, Switzerland

Address for correspondence: Unité de Psychopharmacologie Clinique, Domaine de Belle-Idée, 2, chemin du Petit-Bel-Air, CH-1225 Chêne-Bourg, Switzerland
(e-mail: thierry.steimer@hcuge.ch)

Selected abbreviations and acronyms

ACTH	*adenocorticotropic hormone*
BIS	*behavioral inhibition system*
BNST	*bed nucleus of the stria terminalis*
CeA	*central nucleus of the amygdala*
CRF	*corticotropin-releasing factor*
GABA	*γ-aminobutyric acid*
HPA	*hypothalamo-pituitary-adrenocortical (axis)*
5-HT	*5-hydroxytryptamine (serotonin)*
5-HTT	*serotonin transporter*
LC	*locus ceruleus*
NA	*noradrenaline*
NTS	*nucleus tractus solitarius*
PAG	*periaqueductal gray*
PBR	*peripheral benzodiazepine receptor*
PFC	*prefrontal cortex*
PVN	*paraventricular nucleus*

It is amazing to see how Letourneau's views on emotions, more than a century ago, were in many ways premonitory. The fact that emotions are "intimately linked with organic life," his precise description of the sequence of the physiological and behavioral reactions that accompany a strong emotion, such as fear, the idea that emotions involve specific areas of the brain, and the theory that activation of these areas is associated with an increased blood flow have all been largely confirmed by modern neuroscience. The suggestion that temperament or personality traits influence the "affective style" and vulnerability to psychopathology is also an important aspect of our modern approach to anxiety and mood disorders.[2]

For a long time, emotions were considered to be unique to human beings, and were studied mainly from a philosophical perspective.[3] Evolutionary theories and progress in brain and behavioral research, physiology, and psychology have progressively introduced the study of emotions into the field of biology, and understanding the mechanisms, functions, and evolutionary significance of emotional processes is becoming a major goal of modern neuroscience.

Three fundamental aspects of emotions

The modern era of emotion research probably started when it became obvious that emotions are not just "feelings" or mental states, but are accompanied by physiological and behavioral changes that are an integral part of them. This has progressively led to today's view of emotions being experienced or expressed at three different, but closely interrelated levels: the mental or psychological level, the (neuro)physiological level, and the behavioral level. These three complementary aspects are present in even the most basic emotions, such as fear.

A detailed account of the many "theories of emotion" is beyond the scope of this review. However, a brief historical survey of the more biologically oriented ones may help to set some important conceptual issues.[3-8]

One of the main questions addressed by earlier scientific theories of emotions was whether physiological changes precede the emotional experience, or if they are only a consequence of it. For James (1884) and Lange (1885), "[…] the bodily changes follow directly the perception of the existing fact, and […] our feelings of the same changes as they occur IS the emotion." In other words, according to the James-Lange theory of emotions, stimuli reaching the cerebral cortex induce visceral changes, which are then perceived as emotion. Cannon and Bard (1915–1932) criticized this theory and proposed that the neurophysiological aspects of emotions are subcortical and involve the thalamus.[9] Stimuli from the environment activate the thalamus, which relays information to the cortex and viscera, and back again to the cortex to generate the "emotional state." Watson, the father of behaviorism, was also very critical of what he called the "introverted viewpoint" of James' theory. He considered that there were only three types of unlearned emotional responses, which he called "fear," "rage," and "love" for convenience, although he wanted to "[…] strip them out of all their old connotations."[10] These three emotional responses can be elicited by three sets of specific stimuli. Thus, a sudden noise or loss of physical support can induce an innate fear reaction, and restraint of bodily movements triggers rage. He also mentioned the fact that these emotional responses can be conditioned and that, although these reactions are usually accompanied by specific behaviors, "[…] visceral and glandular factors predominate." Papez's (1937) theory of emotions also had a physiological basis. For him, connections between the cerebral hemispheres and the hypothalamus, and between the cerebral hemispheres and the dorsal thalamus mediate emotions. He held the view that emotion implies behavior (expression) and feeling (experience, subjective aspects). Expression depends on the hypothalamus, and experience on the cortex. Although the "circuit of Papez" is still presented as "the emotional brain" in some handbooks, it is clear

that many details of his original theory are now outdated. More recently, Schachter (1975) emphasized the importance of cognitive processes: bodily states are interpreted in a cognitive context and are modulated by experience. He also showed that the visceral response appears to be a necessary, although not sufficient, condition for the occurrence of emotion.

The view that there is a limited set of emotions (eg, fear, anger, etc) with specific neurophysiological and neuroanatomical substrates that can be considered as "basic" and serve as the primitive building blocks from which the other, more complex emotions are built, was challenged as late as 1990.[11] However, Ekman has convincingly argued that there is now enough evidence of universals in expression and in physiology to suggest a biological basis for these elementary emotions.[12] Panksepp added to these arguments by stating that "genetically dictated brain systems that mediate affective-emotional processes do exist, even though there are bound to be semantic ambiguities in how we speak about these systems."[13]

The biology of fear and anxiety

Fear versus anxiety: is there a difference?

The main function of fear and anxiety is to act as a signal of danger, threat, or motivational conflict, and to trigger appropriate adaptive responses. For some authors, fear and anxiety are undistinguishable, whereas others believe that they are distinct phenomena.

Ethologists define fear as a motivational state aroused by specific stimuli that give rise to defensive behavior or escape.[14] Animals may learn to fear situations in which they have previously been exposed to pain or stress, and subsequently show avoidance behavior when they reencounter that situation. Young animals may show an innate fear reaction to sudden noise or disturbances in the environment, but rapidly become habituated to them. When they are used to a familiar environment, then a fear of novelty may develop. Ethologists have also made the important observation that fear is often mixed up with other aspects of motivation. Thus, conflict between fear and approach behavior may results in displacement activities (eg, self-grooming in rats). Such displacement activities may be the behavioral expression of an anxious state, but anxiety is a concept that is apparently not used by ethologists, perhaps because their definition of fear does in fact include all the more biological aspects of anxiety.

Many authors, however, have argued that differences in their etiologies, response patterns, time courses, and intensities seem to justify a clear distinction between anxiety and fear.[15] Although both are alerting signals, they appear to prepare the body for different actions. Anxiety is a generalized response to an unknown threat or internal conflict, whereas fear is focused on known external danger.[15] It has been suggested that "[…] anxiety can only be understood by taking into account some of its cognitive aspects, particularly because a basic aspect of anxiety appears to be uncertainty. Also, it is reasonable to conclude that anxiety can be distinguished from fear in that the object of fear is 'real' or 'external' or 'known' or 'objective.' The origins of anxiety are unclear or uncertain […]."[3] Other authors pointed out that "[…] situations lacking in clear indications of situational contingencies or likely outcomes are associated with considerable stress. The uncertainty regarding these situations highlights a lack of control that contributes to feelings of anxiety and makes coping more difficult."[15] Barlow has described anxiety as "[…] a unique and coherent cognitive-affective structure within our defensive and motivational system […]. At the heart of this structure is a sense of uncontrollability focused largely on possible future threats, danger, or other upcoming potentially negative events, in contrast to fear, where the danger is present and imminent."[16]

The fact that anxiety and fear are probably distinct emotional states does not exclude some overlap in underlying brain and behavioral mechanisms. In fact, anxiety may just be a more elaborate form of fear, which provides the individual with an increased capacity to adapt and plan for the future.[16] If this is the case, we can expect that part of the fear-mediating mechanisms elaborated during evolution to protect the individual from an immediate danger have been somehow "recycled" to develop the sophisticated systems required to protect us from more distant or virtual threats.

Defense and coping strategies

Fear or anxiety result in the expression of a range of adaptive or defensive behaviors, which are aimed at escaping from the source of danger or motivational conflict. These behaviors depend on the context and the repertoire of the species. Active coping strategies are

used when escape from threat is possible, and the autonomic changes associated with these active strategies are mediated predominantly by sympathetic activation (hypertension, tachycardia). This is the fight-or-flight response originally described by Cannon.[17] Passive coping strategies, such as immobilization or freezing, are usually elicited when threat is inescapable, and are usually characterized by autonomic inhibition (hypotension, bradychardia), and a more pronounced increase in the neuroendocrine response (activation of the hypothalamo-pituitary-adrenal axis and increased glucocorticoid secretion). This type of passive response was originally described by Engel and Schmale as a conservation-withdrawal strategy.[18] The concept of alternative (active/passive) strategies itself owes much to the work of Henry and coworkers.[19] Specific brain circuits appear to mediate distinct coping reactions to different types of stressors.[20,21]

According to Panksepp, flight and other active coping behaviors are unconditional responses to proximate threat, whereas passive coping strategies, such as freezing, are conditioned responses to distal stimuli predictive of danger. These two strategies have distinct and successive roles, and are modulated by the (cognitive) apprehension of the environment and probability of success, eg, whether or not there is a route of escape. Thus, when an animal faces a predator, freezing is preferentially activated when the source of known danger is still far away. When danger gets closer, and the stimulus passes through some critical "psychometric" distance, it becomes a true unconditional stimulus and a flight pattern is activated.[22]

Defensive behaviors have been studied in a large number of species,[23] and it has recently been shown that human defensive behaviors to threat scenarios are not unlike those seen in nonhuman mammals.[24] The importance of risk assessment in making a proper decision about the best strategy to be used in a particular context has been emphasized.[25]

It should be underlined, however, that the choice between an active or passive defense strategy does not entirely depend on contextual clues. Individual differences in coping styles do exist and may also influence this choice. In a given situation, some individuals may react actively ("proactive" style), whereas other individuals may react in a more passive way ("reactive" style). These coping styles are characterized by consistent behavioral and neuroendocrine patterns, and may explain individual differences in vulnerability to stress-induced diseases.[26] Differences in coping styles have also been found between various strains of mice,[27] or between genetically selected rat lines,[28] which suggests that they have a genetic basis.

The capacity to cope successfully with life challenges, whether innate or acquired, is probably a primary determinant of resistance to stress-induced diseases.[29,30]

Normal versus pathological anxiety

Although anxiety is a natural adaptive reaction, it can become pathological and interfere with the ability to cope successfully with various challenges and/or stressful events, and even alter body condition (eg, formation of gastric ulcers).

In 1926, following a major flooding disaster in Leningrad, Pavlov reported a state of "chronic inhibition" and learning impairment in the dogs that had been successfully trained for conditioned responses in his laboratory and had directly experienced the flood.[31] This observation (which may be one of the first laboratory-based accounts of the symptoms of posttraumatic stress disorder) and other experiments were the basis for his later studies on "experimental neuroses" in dogs. Pavlov discovered large differences in dogs' individual susceptibility to psychopathology, and attributed these differences to "nervous types." He described four types analogous to the four temperaments of Hippocrates, which, according to him, resulted from the combination of three factors: the "strength" of the nervous system (its degree of resistance to excitation or inhibition), the equilibrium between excitation and inhibition processes, and the capacity to shift from inhibition to excitation and vice versa.[32]

Although Pavlov's typology is outdated, it is now recognized that increased vulnerability to anxiety and its disorders is associated with particular traits or endophenotypes, ie, traits that may be intermediate in the chain of causality from genes to disease.[33] These traits may be innate or acquired during development or through experience.

Barlow has defined three interacting sets of vulnerability factors for the development of human anxiety disorders in humans: (i) a *generalized biological* vulnerability, mainly of genetic origin; (ii) a *generalized psychological* vulnerability, resulting in particular from early life experiences; and (iii) a *specific psychological* vulnerability, focused on particular events or circumstances.[16] The lat-

ter set is probably implicated in the development of specific anxiety disorders (as opposed to generalized anxiety disorders), ie, social phobia, obsessive-compulsive and panic disorders, and specific phobias.

Increased anxiety in animal models, as a trait, can be attributed to at least two sets of factors: (i) a genetic predisposition, essentially linked to the expression of genes that are involved in the various neurochemical mechanisms underlying fear and anxiety; and (ii) the influence of environmental factors. These environmental factors can interact with the expression of the relevant genes during early development and determine the functional properties of the neural and biochemical systems involved in coping with stressful events. They can also modulate the learning processes that occur at a later stage, when the individual is confronted with various life events, and determine the capacity to cope successfully with aversive or threatening situations in adulthood.

These predisposing factors, either innate or acquired, determine individual "affective styles"[2,34] or coping strategies,[26] which are thought to play an important role in vulnerability to psychopathology.

Animal models

Some of the neurobiological mechanisms underlying anxiety may already be present in very simple organisms, such as the snail *Aplysia*, which can show forms of learning akin to anticipatory and chronic anxiety.[35] However, most animal models of anxiety are based on the use of mammalian species, particularly rats and mice.[36-42] These models fall into two broad categories. In the first one, animals are confronted with situations that generate an anxious state (state anxiety models). This state of anxiety can be either conditioned (eg, conditioned fear, avoidance, and punishment-induced conflict tests) or unconditioned (eg, aversive and ethological conflict tests). In the second category, the models are concerned with trait or "pathological" anxiety: genetic manipulations (transgenic or "knockout" animals) or selective breeding creates lines of rats or mice that permanently express an increased or decreased level of anxiety.

Functional neuroanatomy

As already suspected by Letourneau and others, emotional experience and the associated behavioral responses are likely to activate specific circuits in the brain. The search for the neuroanatomical substrates of fear and anxiety has been a successful field of research over the last decades.

For a long time, it was assumed that emotions, including fear and anxiety, were almost exclusively generated or processed in a "primitive" part of the brain, ie, the limbic system ("the emotional brain"). The view that emotions and cognitions are separate functions of the brain and must therefore have different underlying neuroanatomical substrates is probably responsible for this simplification. As pointed out by LeDoux in a recent review,[43] modern research with the most advanced neuroimaging technologies still uses this dichotomic approach to higher brain functions as a post hoc explanation: "When a so-called emotional task is used, and a limbic area is activated, the activation is explained by reference to the fact that limbic areas mediate emotions. And when a limbic area is activated in a cognitive task, it is often assumed that there must have been some emotional undertone to the task." However, neuroanatomical and behavioral data obtained during the last decades clearly indicate that this dichotomy between cognitive and emotional processes is obsolete.

The locus ceruleus and arousal

Autonomic activation and increased arousal are among the earlier psychophysiological responses observed in a state of fear or anxiety. Since the immediate consequences of autonomic activation (eg, tachycardia) are perhaps the most readily perceived when experiencing a state of fear or anxiety, it has been proposed that the ascending noradrenergic system originating from the locus ceruleus (LC) is the core around which feelings of anxiety are organized.[44] The LC contains a large proportion of the noradrenaline (NA) cell bodies found in the brain and it is a key brain stem region involved in arousal *(Figure 1)*. It is highly responsive to alerting/stressful stimuli. In rats, cats, and monkeys, increased LC neuronal firing rate is associated with alertness, selective attention to meaningful and/or novel stimuli, and vigilance. The meaning, as well as the intensity of stimuli, seems to be an important factor in LC response. In cats, confrontation with a novel, but nonthreatening stimulus, such as a mouse, does not cause a specific increase in LC firing, whereas confrontation with a threatening stimulus (eg, a dog) causes a marked

increase in LC firing. Thus, novelty by itself is not sufficient to activate the LC/NA system, but stimuli that signal reward, as those that signal danger, may activate the system.[45] Recent data suggest that a phasic mode of LC activity may promote focused or selective attention, whereas a tonic mode may produce a state of high behavioral flexibility or scanning attentiveness.[46] Some LC neurons project to the paraventricular nucleus (PVN) in the hypothalamus and activate the hypothalamo-pituitary-adrenocortical (HPA) axis, triggering or facili-

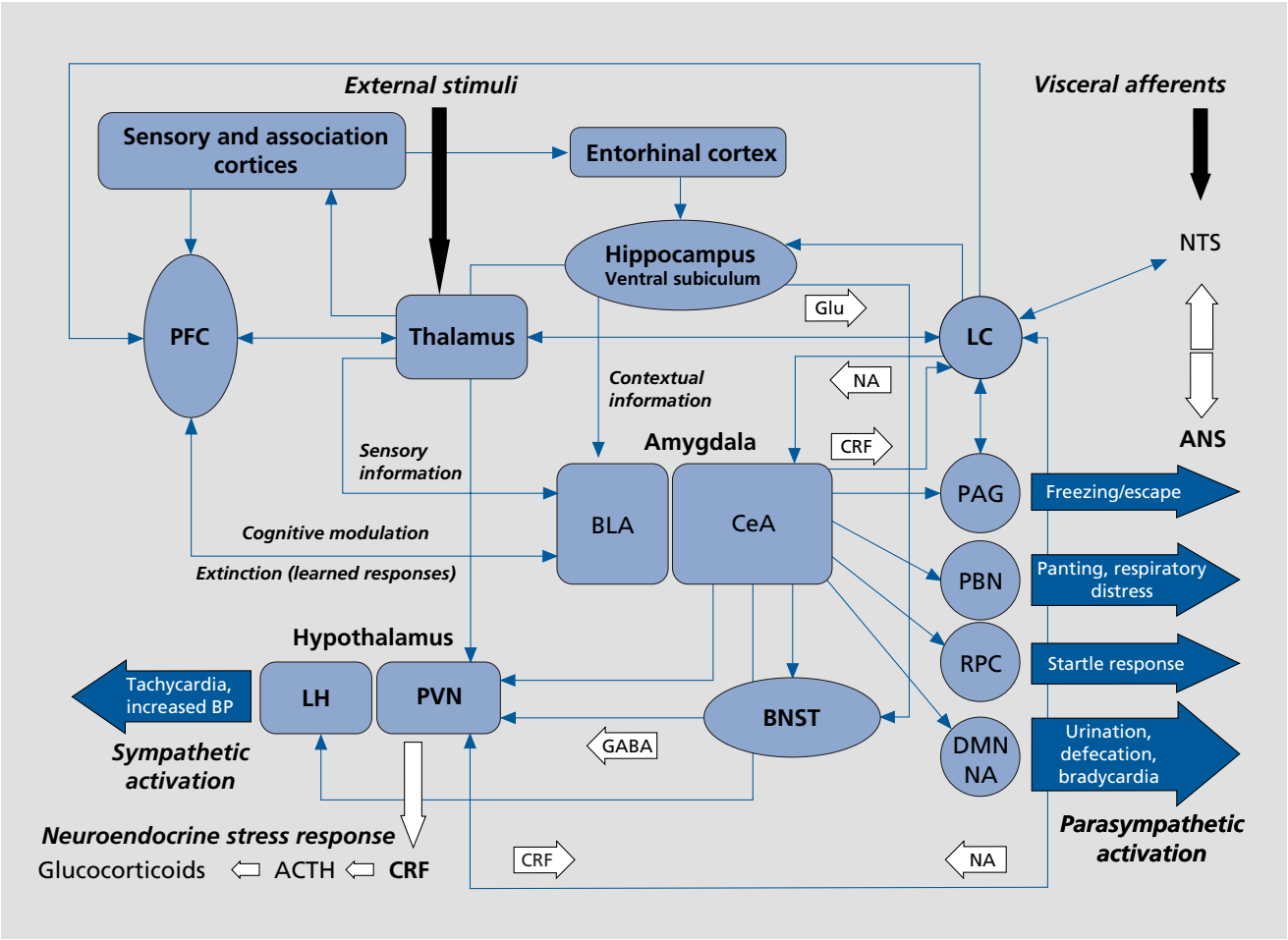


Figure 1. A schematic view of major brain circuits involved in fear and anxiety. External auditory, visual, olfactory, or somatosensory stimuli are relayed by the thalamus to the amygdala and cortex. The basolateral complex (BLA) of the amygdala is the input side of the system, which also receives contextual information from the hippocampal formation (entorhinal cortex, hippocampus, and ventral subiculum). After intra-amygdala processing of the emotional stimuli, the central nucleus of the amygdala (CeA), on the output side, activates the locus ceruleus (LC) and central and peripheral noradrenaline systems (via corticotropin-releasing factor [CRF] neurons), and the hypothalamus (paraventricular nucleus [PVN] and lateral hypothalamus [LH]). The bed nucleus of the stria terminalis (BNST, part of the "extended amygdala") is also a control center for the neuroendocrine system by integrating information originating from both the hippocampus and the amygdala. In addition, the CeA directly activates various midbrain regions or nuclei responsible for different aspects of the fear/anxiety response: freezing or escape (periaqueductal gray [PAG]), increased respiratory rate (parabrachial nucleus [PBN]), startle (caudal reticulopontine nucleus of the reticular formation [RPC]), and the dorsal motor nucleus of the vagus (DMN) in the medulla, which (together with the lateral hypothalamus) is responsible for the increase in heart rate and blood pressure associated with emotional events. The prefrontal cortex (PFC) processes more elaborate ("cognitive") information; it modulates the physiological, neuroendocrine, and behavioral responses (via the amygdala), and it is also involved in the extinction of fear- and anxiety-related conditional responses. ACTH, adrenocorticotropic hormone; ANS, autonomous nervous system; BP, blood pressure; GABA, γ-aminobutyric acid; Glu, glutamate; NA, noradrenaline (neurotransmitter) or nucleus ambiguus (structure); NTS, nucleus tractus solitarius.

tating the stress response associated with increased anxiety *(Figure 1)*. However, although 6-hydroxydopamine lesions of the LC in rats affect the HPA axis response to acute stress, they do not appear to substantially affect its response to chronic stress.[47] Noradrenergic LC neurons also project to the amygdala (mainly to the central nucleus of the amygdala [CeA]), the prefrontal cortex (PFC), the bed nucleus of the stria terminalis (BNST), the hippocampus, the periaqueductal gray (PAG), the hypothalamus, the thalamus, and the nucleus tractus solitarius (NTS), which are all areas involved in the fear/anxiety response *(Figure 1)*. The LC is in turn innervated by areas such as the amygdala (which processes fear-related stimuli) and other areas receiving visceral stimuli relayed by the NTS. The LC is therefore in a key position to integrate both external sensory and internal visceral stimuli and influence stress- and fear-related neuroanatomical structures, including cortical areas.[48]

The septohippocampal system and behavioral inhibition

The inhibition of ongoing behaviors is the first behavioral manifestation of an anxious or fearful state. In the 1970s, Gray suggested that vulnerability to anxiety is associated with individual differences in the activity of a septohippocampal behavioral inhibition system (BIS). According to Gray, this is one of the three major emotional systems, which also include the behavioral approach system (BAS) and the fight/flight system (F/FLS).[49,50] The primary function of the BIS is to compare actual with expected stimuli. If there is a discrepancy between the actual and expected stimuli (ie, "novelty" or "uncertainty"), or if the predicted stimuli are aversive, the BIS is activated, arousal and attention to novel environmental stimuli is increased, and ongoing behaviors are inhibited. Thus, according to Gray, anticipatory anxiety reflects a central state mediated by BIS activation, which is elicited by threats of punishment or failure, and by novelty or uncertainty.[51]

The central role of behavioral inhibition in generating an anxious state has also been pointed out by Laborit.[52] Anxiety is associated with the "alarm reaction," as defined in Selye's original description of the stress response (or general adaptation syndrome).[53] According to Laborit, anxiety appears when one realizes that a proper adaptive action is not possible, ie, that there is loss of control over the situation, and it depends on the activation of the HPA axis.

Panksepp has argued that the activities of the ascending NA systems and the descending BIS are not causally related to the affective experience of fear and anxiety.[22] They may be correlated, supportive, or permissive systems for establishing brain states that participate in the many brain readjustments accompanying fear. These systems certainly participate in the genesis of fear and anxiety behaviors: the NA system is involved in the initial alarm reaction, whereas freezing promoted by septohippocampal inhibition may help regulate the intensity and duration of fear. However, according to Panksepp, the amygdala-central gray axis plays an essential role in creating the emotional state associated with fear and anxiety.[22]

The amygdala-hypothalamus-central gray axis and fear

In all mammalian species, there are three distinct sites in the brain where electrical stimulation will provoke a full fear response: the lateral and central zones of the amygdala, the anterior and medial hypothalamus, and specific areas of the PAG. A circuit coursing from the lateral and central nuclei of the amygdala, throughout the ventral-anterior and medial hypothalamic areas, down to the mesencephalic PAG, may constitute the executive system for fear, since freezing, as well as flight behavior and the autonomic indices of fear (eg, increased heart rate and eliminative behavior) can be evoked along the whole trajectory of this system.[41]

In rats, stepwise increases in the electrical stimulation of the dorsolateral periaqueductal gray (dlPAG) produce alertness, then freezing and finally escape, replicating the sequence of natural defensive reactions when exposed to threat. Recent data suggest that dlPAG stimulation produces freezing independently of any contextual fear conditioning, whereas stimulation of the ventral periaqueductal gray (vPAG) appears to be critical to the expression of conditioned fear.[54] Because electrical or pharmacological stimulation of PAG produces a range of fear-related responses similar to those seen in a panic attack, this area be could be directly implicated in panic disorder.[55,56]

The amygdala and fear conditioning

The elegant studies carried out by LeDoux, based on a simple fear conditioning paradigm in rats, have emphasized the primary role of the amygdala in controlling

emotional behaviors.[43,57-59] His approach is along the lines of earlier learning/behavioral theories, eg, those of Pavlov and Watson,[3] which emphasize the role of conditioning processes in behavioral development. After a few pairings of a threatening stimulus (eg, electric shocks, the unconditioned stimulus [US]) with a formerly neutral cue (eg, a tone or visual signal, the conditioned stimulus [CS]), animals will experience a state of conditioned fear when only the cue is present. Conditioned fear provides a critical survival-related function in the face of threat by activating a range of protective (or defensive) behaviors. The neuroanatomical and neurochemical foundations of conditioned fear,[60] based mainly on the behavioral models of freezing and fear-potentiated startle in rats[61] have been worked out in detail. In LeDoux's model, the amygdala and thalamic pathways are responsible for the primary appraisal of threat by allowing a rapid, automatic analysis of potentially dangerous stimuli. Additional brain structures, including the hippocampus and cortical pathways, provide more information on the situational context and relevant stimulus characteristics *(Figure 1)*. Thus, the amygdala plays a central role by integrating rapid, direct thalamic inputs, eg, visual information, with more detailed information, eg, cortical integration of sensory information, originating from longer and slower neuronal pathways.[43] Activation of the amygdala by threatening stimuli then influences cognitive processes, perception, selective attention, and explicit memory.

The cognitive representation of fear may preferentially involve the left amygdala, as shown by recent functional magnetic resonance imaging (fMRI) studies.[62] Interestingly, a sex difference in amygdala activation during the perception of facial affect has recently been reported.[63] Amygdala activation (measured by fMRI) differed for men and women depending on the valence of the expression: happy faces produced greater right than left amygdala activation for males, but not for females. Both sexes showed greater left amygdala activation for fearful faces. These data suggest that the left amygdala may be more involved in the representation of negative affect.

The role of the various amygdala nuclei in fear conditioning is now well established, notably by lesion studies.[43,59,60,64] In rats, the central and medial nuclei of the amygdala are important in mediating conditioned aversive states, but conditioned freezing may be mediated independently.[65] Thus, different types of fear-conditioned behavior may be mediated by separate nuclei within the amygdala.[66]

The amygdala plays a pivotal role in coordinating the behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in rats. In a fear-conditioning paradigm, pretraining amygdala lesions blocked freezing behavior, ultrasonic vocalizations, adrenocortical activation, and dopaminergic metabolic activation in the medial prefrontal cortex (mPFC). Posttraining lesions blocked mPFC dopamine, serotonin (5-hydroxytryptamine [5-HT]), and NA activation and stress-induced freezing and defecation, and greatly attenuated adrenocortical activation.[67]

The amygdala and positive reinforcement and attention

The role of the amygdala is not limited to fear-conditioning and the processing of aversive stimuli. Studies in rats using food-motivated associative learning indicate that the basolateral amygdala may be involved in the acquisition and representation of positive reinforcement values (possibly through its connections with the ventral striatal dopamine systems and the orbitofrontal cortex).[68] Therefore, the amygdala is probably a key structure for the integration of behavior in conflicting situations, when both potentially rewarding and aversive stimuli are present. Recent studies indicate that the human amygdala can also process both positively and negatively valenced stimuli.[69]

Recent studies also indicate that the CeA may contribute to attentional function in conditioning, by way of its influence on basal forebrain cholinergic systems and on the dorsolateral striatum.[68]

The amygdala and social behavior and phobia

The amygdala may play an important role in regulating social behavior. Thus, in adult macaque monkeys, selective bilateral lesions of the amygdala result in a lack of fear response to inanimate objects and a "socially uninhibited" pattern of behavior.[70] The amygdala may function as a protective "brake" during evaluation of a potential threat, and it has been suggested that social anxiety may involve a dysregulation or hyperactivity of the amygdala evaluative process.[70] Studies in rats also suggest that the basolateral nucleus of the amygdala may play a crucial role in the consolidation of information that leads to the formation of a specific phobia.[71]

The extended amygdala (BNST) and anxiety

Although the amygdala is clearly involved in conditioned fear, its role in anxiety is less evident, because it is often difficult to specify the stimuli that triggers anxiety.[72,73] Thus, lesions of the rat amygdala that suppressed fear-elicited startle or freezing behavior did not affect measures of anxiety in the elevated plus-maze and shock-probe–burying tests, two classic tests of anxiety for rodents.[74] Moreover, diazepam was effective in these tests, even in amygdala-lesioned rats, suggesting that the anxiolytic effects of benzodiazepines are not necessarily mediated by the amygdala.[75] Recent studies in primates also suggest that the amygdala is involved in mediating some acute unconditioned fear responses in rhesus monkeys, but that it is unlikely to be a key structure regarding the dispositional behavioral and physiological characteristics of the anxious temperament.[76]

The BNST is considered to be part of the extended amygdala.[77] It appears to be a center for the integration of information originating from the amygdala and the hippocampus *(Figure 1)*, and is clearly involved in the modulation of the neuroendocrine stress response.[78,79] Activation of the BNST, notably by corticotropin-releasing factor (CRF), may be more specific for anxiety than fear. Studies in rats with the startle reflex suggest that explicit cues such as light, tone, or touch activate the amygdala, which then activates hypothalamic and brainstem target areas involved in the expression of fear, whereas less specific (or more complex) stimuli of longer duration, such as exposure to a threatening environment or intraventricular administration of CRF, may preferentially involve the BNST.[73]

The PFC and the control of emotional responses

The primary roles of the PFC appear to be the analysis of complex stimuli or situations and the control of emotional responses.

In a revised version of his original BIS model, Gray postulated that the PFC may modulate septohippocampal activity, and that lesions to this area would impair the processing of vital information for the subicular comparator, and subsequently affect behavioral inhibition and anticipatory anxiety.[51] He also suggested that the role of cortical structures in anxiety was probably more prominent in primates, based on the increased anatomical relationship between the septohippocampal system and the prefrontal and cingulate cortices observed in monkeys. Recent studies in humans and primates have largely confirmed Gray's hypothesis, and it is now clear that the various subdivisions of the human PFC (dorsolateral, ventromedial, and orbital sectors) have specific roles in representing affect in the absence of immediate rewards or punishments and in controlling emotional responses.[80,81] There appear to be important functional differences between the left and right sides within each of these sectors. Earlier studies on patients with unilateral brain lesions have already emphasized the role of cerebral lateralization in emotional information processing.[82] More recently, brain electrical activity measures and positron emission tomography (PET) studies have indicated that negative affect and anxiety are associated with increased activation of the right PFC; moreover, individual differences in baseline levels of asymmetric activation in the PFC may be associated with individual differences in affective styles and vulnerability to mood and anxiety disorders.[81]

There is also increasing evidence that the PFC plays an important role in controlling anxiety and the associated stress response in rats, and that cerebral laterality is an important feature of the PFC system. Thus, in a recent study right, but not left, lesions of the ventral medial PFC were shown to have anxiolytic effects, and were also more effective in suppressing the neuroendocrine and autonomic stress response.[83]

Neurochemical correlates

A large number of neurotransmitters, peptides, hormones, and other neuromodulators have been implicated in fear and anxiety. We shall only discuss a few representative examples.

The noradrenergic system

Several preclinical studies have shown that stress and anxiety cause a marked increase in NA release in several rat brain regions, including the hypothalamus, the amygdala, and the LC.[84]

In agreement with these data, yohimbine, an α_2-adrenergic receptor antagonist that increases NA release in the brain, has been shown to have anxiogenic effects in rats.[84] However, pharmacological experiments involving the administration of various α_{2A}-receptor agonists or antagonists in several animal models of anxiety are

inconsistent, perhaps due to their interaction with other monoaminergic receptors.[85] In a recent study, local administration into the LC region of an antisense oligodeoxynucleotide (AS-ODN) corresponding to the α_{2A}-receptor mRNA was shown to have an anxiolytic effect,[85] but another study has also shown that genetic knockout of the α_{2A}-receptor in mice resulted in a *more anxious* phenotype than that of the corresponding C57BL/6 wild type.[86]

The role of the various NA receptor subtypes in mediating NA action on fear- and anxiety-related behaviors is therefore not settled. The precise location of the receptor subtypes within the complex circuitry mediating fear and anxiety responses is probably critical.

The serotonergic system

Data on the role of 5-HT in anxiety are conflicting: there is no agreement whether 5-HT enhances or, conversely, decreases anxiety. Thus, a 5-HT_{2C} agonist such as *m*-chlorophenylpiperazine (mCPP) has anxiogenic effects in humans and may induce panic attacks, obsessions, and other neuropsychiatric symptoms, whereas selective 5-HT reuptake inhibitors (SSRIs) and 5-HT_{1A} or 5-HT_3 receptor–selective drugs can have antianxiety effects in certain anxiety disorders and animal models.[87]

On the basis of data obtained from animal models, Graeff et al have proposed a "dual 5-HT fear hypothesis" postulating that 5-HT may enhance conditioned fear in the amygdala, while inhibiting innate fear in the dorsal PAG.[88] The ascending 5-HT pathway originating from the dorsal raphe nucleus (DRN) and innervating the amygdala and frontal cortex facilitates conditioned fear, while the DRN-periventricular pathway innervating the periventricular and PAG matter inhibits inborn fight/flight reactions to impending danger, pain, or asphyxia.[89] The same authors have also proposed that the pathway connecting the median raphe nucleus (MRN) to the hippocampus may promote resistance to chronic, unavoidable stress by facilitating hippocampal 5-HT_{1A} transmission.[89]

These results demonstrate that it is not possible to conclude about an "anxiogenic" or "anxiolytic" role for 5-HT (or, for that matter, of any other neurotransmitter, peptide, or hormone) without considering its site of action in the brain and/or the receptor subtype implicated.

Indirect evidence that the anxiolytic action of 5-HT is mediated by the 5-HT_{1A} receptor has been obtained by three independent groups who have reported an "anxious" phenotype in 5-HT_{1A} receptor knockout mice compared with corresponding wild-type mice, using three different genetic backgrounds.[90] Depending on this background, the null mutation may be associated with changes in GABAergic transmission.[91] More recently, it has been shown that 5-HT_{1A} receptor knockouts display an "anxious-like" phenotype not only at the behavioral, but also at the autonomic response level.[92] This seems to provide a strong argument in favor of an important role of 5-HT_{1A} receptor gene expression for anxiety-related behaviors. In contrast, 5-HT_{1B} receptor knockout mice were found to be more aggressive, more reactive, and less anxious than their wild-type counterparts, suggesting that this receptor may also modulate 5-HT action on defense mechanisms.[93] Serotonin transporter (5-HTT) knockout mice (5-HTT-/-) have also been produced, and shown to display elevated anxiety in various behavioral tests, and an increased stress response (adenocorticotropic hormone [ACTH] secretion) following a mild stress, which was also observed to a lesser degree in the 5-HTT+/- heterozygotes.[94]

The GABAergic system

γ-Aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the brain. The $GABA_A$-benzodiazepine receptor is an important target for several anxiolytic drugs and may therefore play an important role in anxiety-related disorders.[95] Several $GABA_A$ receptor subtypes have been described.[96,97]

The diazepam-sensitive α_2-$GABA_A$ subtype appears to be specifically involved in anxiolysis.[96] This subtype is largely expressed in the hippocampus, the amygdala, and the striatum.[98] Two mouse lines were generated with a knockin point mutation on the α_2 or α_3 subunit, which rendered them insensitive to diazepam. The anxiolytic action of diazepam was suppressed in mice with the α_2(H101R) point mutation, but not in those with the α_3(H126R) point mutation.[99]

Heterozygous γ2-knockout mice (γ2+/-) have been generated (the homozygous mutation is not viable).[98] These mice show enhanced reactivity to natural aversive stimuli, increased passive avoidance responses, and a deficit

in ambiguous cue discrimination.[100] They have been proposed as a model for trait anxiety characterized by harm avoidance behavior and explicit memory bias for threat cues (enhanced sensitivity to negative associations).
In contrast to the anxiolytic action of benzodiazepine-like compounds, inverse agonists of the GABA/benzodiazepine receptor such as the β-carbolines are well known to be anxiogenic. Recently, intrahippocampal injections of a novel inverse agonist (RY024) have been shown to produce a fear response (freezing) and to interfere with fear-conditioning in rats.[101]

The neurosteroids

The neurosteroids are a novel, interesting class of neuromodulators synthesized in the brain directly from cholesterol.[102] They appear to act essentially via an allosteric modulation of the $GABA_A$ receptor, although other receptors may also be involved.[102,103] As early as 1987, Majewska suggested that neurosteroids could play an important role in mood regulation.[104] Several studies have shown that positive allosteric modulators (which potentiate GABA action), such as progesterone and allopregnanolone, have anxiolytic effects in various animal models.[103] Neurosteroid synthesis is regulated by a peripheral benzodiazepine receptor (PBR) located on the outer mitochondrial membrane,[105] and part of the anxiolytic effects of benzodiazepine could in fact involve increased neurosteroid synthesis. Compounds with a selective affinity for the PBR, such as FGIN-1-27, have shown an anxiolytic action in rats.[106] Neurosteroids are currently attracting a lot of interest because of their potential role as natural, endogenous anxiolytics.

Hormones of the HPA axis

Hormones of the HPA axis, such as cortisol, or corticosterone (in rodents), ACTH, and CRF are usually increased in a state of fear and anxiety. They also appear to modulate the response to threatening events.

Corticotropin-releasing factor

Intracerebral administration of CRF has been shown to elicit anxious-like behavior in rats.[107] More recent preclinical studies suggest that CRF and its receptors play a pivotal, integrative role in the stress response and anxiety-related behaviors.[108,109] There are two major CRF systems in the brain: the neuroendocrine system in the PVN, and another system with CRF cells located in the amygdala (CeA) and BNST, which would be more directly related to the physiological and behavioral responses associated with fear and anxiety. Whereas glucocorticoids restrain CRF production in the PVN (the neuroendocrine negative feedback loop), they appear to increase CRF expression in the amygdala and BNST, thus promoting fear- and anxiety-related behavior.[110] CRF neurons originating from the amygdala project onto the LC *(Figure 1)* and contribute to increased arousal in fear and anxiety states.[111] In a rat model, a full postsynaptic CRF agonist, CRF(1-41), increased arousal at low dosage and had an anxiogenic action at higher doses.[112] This suggests that progressively increasing levels of CRF in the brain may ensure the transition from the initial state of increased arousal to the anxious state of expectancy in stressful situations.
Transgenic mice overexpressing CRF show a behavioral and neuroendocrine profile consistent with an increased level of stress and anxiety, including elevated plasma ACTH and corticosterone levels, and generally exhibit the same behavioral changes as those observed in mice following exogenous CRF administration.[113-115] Recent data indicate a desensitization of postsynaptic, but not presynaptic $5\text{-}HT_{1A}$ receptors in mice overproducing CRF.[116] Another line of transgenic mice overexpressing CRF (CRH-OE(2122)) has shown a reduced startle reactivity, habituation, and prepulse inhibition.[117]
Deletion of the CRF gene (CRF-KO mice) results in chronic glucocorticoid insufficiency, and this may cause severe developmental problems.[114,118] Despite an impaired stress-induced activation of the HPA axis, the behavioral stress responses do not appear to be markedly affected in CRF-deficient mice, suggesting that other CRF-like molecules may be implicated in the behavioral effects mediated by CRF receptors.[114,118-120] CRF-KO mice also display normal startle- and fear-conditioned responses.[120]

CRF receptors and CRF binding protein

Deletion of the genes coding for CRF receptors 1 *(CRF-R1)* or 2 *(CRF-R2)* have more profound behavioral effects.[114,115,121-124] *CRF-R1*-deficient mice display decreased anxiety and an impaired stress response,[125] whereas deletion of the *CRF-R2* gene has the reverse effect in males (but not in females): anxiety is increased in Crhr2-/-.[126] These data suggest that *CRF-R1* mediates the anxio-

genic effects of CRF, whereas *CRF-R2* may be involved in anxiolysis. Recently, mice deficient in both CRF-R1 and CRF-R2 receptors have been generated.[127] These double mutants display altered anxiety-related behavior and an impaired HPA axis response to stress. Interestingly, the effects on anxiety are again sex-dependent: females show a decreased anxiety similar to that observed in Crhr1-/- mutants, whereas the genotype has no effect on male anxiety-related behaviors. These studies have also demonstrated a novel role of the mother's genotype on the development of pup anxiety: pups born to a heterozygous or mutant mother display significantly more anxiety, regardless of that pup's genotype.[127]
The CRF binding protein (CRF-BP) may play an important modulatory role in CRF action.[128] Interesting data consistent with a modulatory action of CRF-BP have recently been obtained with transgenic and knockout models: transgenic males overexpressing CRF-BP tend to show less anxiety, whereas the behavior of CRF-BP-deficient mice was consistent with increased anxiety.[129]

Corticosteroids

Corticosteroids effects on anxiety-related behaviors may be mediated by both genomic and nongenomic mechanisms (control of neuronal excitability). Hippocampal corticosteroid receptors play an important role in the termination of the acute stress response.[130] Studies with a model of posttraumatic stress disorder in rats suggest an alteration of the mineralocorticoid receptor (MR) vs glucocorticoid receptor (GR) balance, as measured by the expression of mRNA levels in the hippocampus, during the recovery phase following acute stress: the MR/GR ratio was decreased, but only in animals with an enhanced fast feedback.[131] Recent data also suggest that, at low circulating levels, corticosteroids exert a permissive action (via MRs) on acute freezing behavior and other acute fear-related behaviors. At higher levels, corticosteroids enhance acquisition, conditioning, and consolidation of an inescapable stressful experience, as well as processes underlying fear potentiation, via GR-dependent mechanisms.[132] Mice with targeted mutation of the MR and GR receptors display altered anxiety-related behaviors.[133]

Other peptides, neurotransmitters, and hormones

Several peptides, such as cholecystokinin (CCK), neuropeptide Y (NPY), tachykinins (substance P, neurokinins A and B), and natriuretic peptides (atrial natriuretic peptide or C-type natriuretic peptide) may play important roles in fear- and anxiety-related behaviors.[134] CCK may be particularly relevant for panic disorders,[135,136] and may influence cognitive processes.[137]
Excitatory amino acids (EAA), such as glutamate, are also important. In rats, microinjections of EAA into the dorsolateral PAG induce a flight reaction. Part of the effects mediated by *N*-methyl-D-aspartate (NMDA) receptors may involve nitric oxide (NO). Nitric oxide synthase (NOS) inhibitors injected in the dorsolateral PAG have been shown to have anxiolytic effects, and psychological stress (restraint) induced an increased expression of neuronal NOS in the same area and in other areas related to defense mechanisms, suggesting that NO may participate in these defensive responses.[138]
We have also shown that anticipatory anxiety can lead to a decreased secretion of luteinizing hormone (LH) and testosterone in young, healthy male subjects.[139]

Genetic and environmental factors

Individual differences in sensitivity to threat or stress, and particular coping or affective styles appear to be critical predisposing factors for anxiety-related disorders. Genetic and environmental factors have been implicated, and how these factors interact during development is one of the major questions addressed by recent clinical and fundamental research.

Genetic determinants

A genetic basis for anxiety-related behaviors is now clearly established, notably through several family, twin, and adoption studies.
In mice, targeted gene mutations have shown that modifying the expression of particular genes can have a profound effect on anxiety-related behavioral phenotypes.[39,140] Some examples were mentioned in the preceding section.
Natural variations in trait anxiety, or emotionality, in inbred rat and mouse strains are being extensively studied.[27,39,141-146] Some of these strains show differences in sensitivity to anxiolytic agents such as diazepam.[147,148] Cross-breeding of inbred rodents strains has shown the quantitative nature of many anxiety-related traits.[149,150]
The quantitative trait locus (QTL) method is based on a comparison between the allelic frequency of DNA

markers and quantitative behavioral traits.[146,150] It has been used to assess gene effects on fear, emotionality, and anxiety-related behaviors in mice from various genetic backgrounds.[140,151] Loci on mouse chromosomes 1, 4, and 15 were found to operate in four tests of anxiety, whereas loci on chromosomes 7, 12, 14, 18, and X influenced only a subset of behavioral measures.[152] A QTL influencing anxiety has also been found recently on rat chromosome 5.[153]

Selective breeding of mice and rats has also been used to create lines that show extreme behavioral characteristics within the range of the normal population.[140] Various selection criteria can be used, which may not be directly related to anxiety. Thus, rat lines initially selected for their good versus poor performance in two-way, active avoidance were subsequently shown to differ in trait anxiety, or emotionality. For instance, the Roman high- (RHA/Verh) and low- (RLA/Verh) avoidance rat lines display clear differences in emotionality and anxiety-related behaviors.[28,154] The more anxious (RLA/Verh) rats display increased neuroendocrine and autonomic reactivity to mild stressors.[28,155,156] Differences in vasopressin, oxytocin, and CRF action at the level of the amygdala,[156,157] dopaminergic and GABAergic neurotransmission,[158] basal vasopressin mRNA expression in the hypothalamic PVN,[159] and 5-HTT levels in the frontal cortex and hippocampus[160] have been reported. We have shown an increased capacity (enzymatic activities) for the production of progesterone-derived, anxiolytic neurosteroids in the frontal cortex and BNST of RHA/Verh rats, which may explain in part the differences in emotional reactivity of these two lines.[28] These two rat lines also differ in their respective coping styles and response to novelty,[154,155] and this model may therefore prove useful for studying the interaction between anxiety and defense mechanisms.

Recently, two Wistar rat lines have been selected and bred for high anxiety-related behavior (HAB) or low anxiety-related behavior (LAB) on the elevated plus-maze, a classical test for anxiety in rodents.[149] The neuroendocrine, physiological, and behavioral characteristics of these two lines are being extensively studied, and show some similarities, but also differences, as compared to the Roman rat lines.[161-167] Further comparison between lines such as the RHA/RLA and HAB/LAB rats, which have been selected on different behavioral criteria (avoidance versus anxiety in the elevated plus-maze test), but show a similar, anxiety-related behavioral phenotype, may be extremely fruitful to delineate brain mechanisms underlying specific aspects of anxiety disorders.

Environmental influences

The role of environmental influences in the etiology of anxiety is also well established.[15] Early adverse experience is a major developmental risk factor for psychopathology.[168-170]

Prenatal stress in animal models has been shown to permanently alter brain morphology, anxiety-related behavior, coping, and regulation of the HPA axis in adulthood.[171] Naturally occurring variations in maternal care can also alter the regulation of genes controlling the behavioral and neuroendocrine responses to stress, as well as hippocampal synaptic development. These effects are responsible for stable, individual differences in stress reactivity, as well as the maternal behavior of female offspring.[172] They could constitute the basis of a nongenetic mechanism for the transmission of individual differences in stress reactivity and coping styles across generations.

In 1958, Levine reported that rats handled for the first 21 days of life exhibit reduced fearfulness compared with nonhandled controls. Since then, several studies have shown the beneficial effects of neonatal handling and a progressive habituation to stress on adults' stress responses and anxiety-related behaviors. Neonatal handling can even reverse the behavioral abnormalities induced by prenatal stress.[173] These effects appear to be mediated essentially by the CRF/HPA axis system,[174,175] although the serotonergic and catecholaminergic systems could be also involved.[176,177] A study has shown that neonatal handling increases the expression of the peripheral benzodiazepine receptor (PBR), which has been implicated in the synthesis of endogenous, natural anxiolytic agents such as the neurosteroids, in rat adrenals, kidney, and gonads.[178] It is likely that increased adrenal production of naturally anxiolytic compounds such as allopregnanolone contributed to the decrease in anxiety reported in this study.

Sex differences in the effects of neonatal handling have been recently reported: neonatal handling may provide males with a greater capacity to actively face chronic stressors.[179] Recent data indicate that neonatal handling can also affect memory processes involved in contextual fear conditioning.[180]

In the Roman rat lines, neonatal handling has been shown to alter the behavioral phenotype of the more anxious

RLA/Verh rats so that, in adulthood, they behave in the same way as their nonhandled, hypoemotional RHA/Verh counterparts. Females were found to be more sensitive than males to the positive influences of early stimulation.[181] The effects of neonatal handling on RLA/Verh rats were not limited to behavioral stress responses and coping behaviors, but were accompanied by a concomitant decrease in stress-induced ACTH, corticosterone, and prolactin release, indicating that the neurochemical substrates underlying these responses were also permanently affected by early experience.[182,183]

This and other examples indicate that the developmental processes that determine individual sensitivity to stressors, or emotionality, and coping behaviors involve complex interactions between genetic and environmental factors, and that anxiety-related phenotypes cannot be predicted on the sole basis of a genetic predisposition or early adverse experience.

Conclusions

The biological bases of fear and anxiety are now recognized, and the major brain structures and neuronal circuits involved in emotional information processing and behavior are delineated. Emotional and cognitive processes cannot be dissociated, even when considering such a basic emotion as fear. The cognitive apprehension of events and situations is critically involved in emotional experiences and also influences coping strategies or defense mechanisms. This is reflected in the important role now attributed to the PFC in controlling emotional behavior in humans and animals.

Molecular biology techniques, such as those used to create transgenic and knockout mice, have been successful in exploring the role of various neurotransmitters, peptides, hormones, and their receptors in mediating the appraisal of stressful stimuli, information processing through the various neuronal circuits, and the physiological responses and behaviors associated with fear and anxiety.

It is now clear that individual differences in affective or coping styles, which are also observed in nonhuman species, are directly associated with vulnerability to psychopathology. Studying these individual differences, including sex-related differences, in humans and in animal models will give interesting clues about the brain mechanisms of emotional behavior.

Finally, the study of genetic predisposition and environmental influences, particularly during early development, in determining vulnerability traits and anxiety-prone endophenotypes is certainly becoming one of the major, and perhaps most promising, domains of contemporary research with respect to our understanding of the etiology of anxiety and mood disorders. ❑

The author would like to express his gratitude to the Swiss National Science Foundation for supporting work on the Roman rat lines in his laboratory (grant 32-51187-97).

REFERENCES

1. Letourneau C. *Physiologie des passions*. 2nd ed. Paris, France: C. Reinwald & Cie; 1878.
2. Davidson JR. Affective style, mood and anxiety disorders. An affective neuroscience approach. In: Davidson JR, ed. *Anxiety, Depression and Emotions*. Oxford, UK: Oxford University Press; 2000:88-108.
3. Strongman KT. *The Psychology of Emotion. Theories of Emotion in Perspective*. Chichester, UK: John Wiley & sons; 1996.
4. Ekman P, Davidson RJ (eds). *The Nature of Emotion*. Oxford, UK: Oxford University Press; 1994.
5. Panksepp J. *Affective Neuroscience*. New York, NY: Oxford University Press; 1998.
6. Borod JC (ed). *The Neuropsychology of Emotion*. Oxford, UK: Oxford University Press; 2000.
7. Davidson JR (ed). *Anxiety, Depression, and Emotion*. Oxford, UK: Oxford University Press; 2000.
8. Lewis M, Haviland-Jones JM (eds). *Handbook of Emotions*. New York, NY: The Guilford Press; 2000.

La biología de las conductas relacionadas con el miedo y la ansiedad

La ansiedad es una condición psicológica, fisiológica y conductual que se induce en los animales y en el hombre por una amenaza al bienestar o a la sobrevivencia, sea presente o potencial. Se caracteriza por un aumento del alerta, expectación, activación autonómica y endocrina, y patrones conductuales específicos. La función de estos cambios es facilitar la adaptación ante una situación adversa o inesperada. La ansiedad patológica interfiere con la capacidad para adaptarse exitosamente a los desafíos de la vida. La vulnerabilidad a la psicopatología parece ser una consecuencia de factores predisponentes (o rasgos) los cuales se deben a numerosas interacciones entre los genes y el ambiente durante el desarrollo (especialmente durante el período perinatal) y a lo largo del curso de la vida (acontecimientos vitales). En esta revisión se examinará la biología del miedo y la ansiedad desde aproximaciones sistémicas (relaciones cerebro-conducta, circuitos neuronales y neuroanatomía funcional) y moleculares/celulares (neurotransmisores, hormonas y otros factores bioquímicos) poniendo especial atención a los modelos animales. Estos modelos han constituido un medio para establecer los correlatos biológicos del miedo y la ansiedad; sin embargo, el reciente desarrollo de métodos de investigación no invasores en humanos, como las diversas técnicas de neuroimágenes, ciertamente abre nuevas vías de investigación en este campo. Nuestro conocimiento actual de las bases biológicas del miedo y la ansiedad ya es notable y se puede esperar que a futuro se progrese hacia modelos o teorías que integren contribuciones desde las ciencias médicas, biológicas y psicológicas.

Biologie des comportements liés à l'anxiété et à la peur

L'anxiété est un état psychologique, physiologique et comportemental provoqué chez les animaux et les humains par une menace qui s'exerce sur le bien-être ou la survie, qu'elle soit réelle ou potentielle. Elle est caractérisée par une hypervigilance, une attente excessive, une activation des systèmes autonome et neuroendocrine et par des schémas comportementaux spécifiques. Ces modifications doivent faciliter l'adaptation à une situation hostile ou inattendue. L'anxiété pathologique interfère avec la capacité de s'adapter avec succès aux aléas de la vie. La susceptibilité à la psychopathologie semble résulter de facteurs prédisposants (ou de caractères), eux-mêmes issus de nombreuses interactions gène-environnement pendant la phase de développement (particulièrement durant la période périnatale) et de l'expérience (événements de la vie). Dans cet article, la biologie de la peur et de l'anxiété sera examinée d'un point de vue systémique (relations cerveau-comportement, circuits neuronaux et neuroanatomie fonctionnelle) et d'un point de vue cellulaire et moléculaire (neurotransmetteurs, hormones et autres facteurs biochimiques), avec une référence particulière aux modèles animaux. Ces modèles ont contribué à l'établissement de corrélations biologiques de la peur et de l'anxiété, bien que les avancées récentes des méthodes d'investigation non invasives chez les humains, telles les diverses techniques de neuroimagerie, ouvrent certainement de nouvelles voies de recherche dans ce domaine. Nos connaissances actuelles des bases biologiques de la peur et de l'anxiété sont déjà impressionnantes et nous pouvons espérer des progrès supplémentaires de la part de modèles ou de théories intégrant les données des sciences médicales, biologiques et psychologiques.

9. Cannon WB. The James-Lange theory of emotions: a critical examination and an alternative theory. By Walter B. Cannon, 1927. *Am J Psychol*. 1987;100:567-586.
10. Watson JB. *Behaviorism*. 7th ed. New York, NY: WW Norton & Company; 1970.
11. Ortony A, Turner TJ. What's basic about basic emotions? *Psychol Rev*. 1990;97:315-331.
12. Ekman P. Are there basic emotions? *Psychol Rev*. 1992;99:550-553.
13. Panksepp J. A critical role for "affective neuroscience" in resolving what is basic about basic emotions. *Psychol Rev*. 1992;99:554-560.
14. McFarland D. *The Oxford Companion to Animal Behaviour*. Oxford, UK: Oxford University Press; 1987.
15. Craig KJ, Brown KJ, Baum A. Environmental factors in the etiology of anxiety. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: the Fourth Generation of Progress*. New York, NY: Raven Press; 1995:1325-1339.
16. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *Am Psychol*. 2000;55:1247-1263.
17. Cannon WB. *Bodily Changes in Pain, Hunger, Fear and Rage*. New York, NY: Appleton; 1915.

18. Engel GL, Schmale AH. Conservation withdrawal: a primary regulatory process for organic homeostasis. In: *Physiology, Emotions and Psychosomatic Illness*. New York, NY: Elsevier; 1972:57-95.
19. Henry JP, Stephens PM. *Health and the Social Environment: a Socio-biological Approach to Medicine*. Berlin, Germany: Springer; 1997.
20. Keay KA, Bandler R. Parallel circuits mediating distinct emotional coping reactions to different types of stress. *Neurosci Biobehav Rev*. 2001;25:669-678.
21. Bandler R, Price JL, Keay KA. Brain mediation of active and passive emotional coping. In: Mayer EA, Sapers CB, eds. *Progress in Brain Research*. Vol 122. Amsterdam, The Netherlands: Elsevier Science BV; 2000:333-349.
22. Panksepp J. The psychoneurology of fear: evolutionary perspectives and the role of animal models in understanding human anxiety. In: Burrows GD, Roth M, Noyes Jr R, eds. *Handbook of Anxiety. Volume 3. The Neurobiology of Anxiety*. Amsterdam, The Netherlands: Elsevier Science BV; 1990:3-58.
23. Bakshi VP, Shelton SE, Kalin NH. Neurobiological correlates of defensive behaviors. In: Mayer EA, Sapers CB, eds. *Progress in Brain Research*. Vol 122. Amsterdam, The Netherlands: Elsevier Science BV; 2000:105-115.
24. Blanchard DC, Hynd AL, Minke KA, Monemoto T, Blanchard RJ. Human defensive behaviors to threat scenarios show parallels to fear- and anxiety-related defense patterns of non-human mammals. *Neurosci Biobehav Rev*. 2001;25:761-770.
25. Kavaliers M, Choleris E. Antipredator responses and defensive behavior: ecological and ethological approaches for the neurosciences. *Neurosci Biobehav Rev*. 2001;25:577-586.
26. Koolhaas JM, Korte SM, De Boer SF, et al. Coping styles in animals: current status in behavior and stress-physiology. *Neurosci Biobehav Rev*. 1999;23:925-935.
27. Parmigiani S, Palanza P, Rodgers J, Ferrari PF. Selection, evolution of behavior and animal models in behavioral neuroscience. *Neurosci Biobehav Rev*. 1999;23:957-970.
28. Steimer T, Driscoll P, Schulz P. Brain metabolism of progesterone, coping behaviour and emotional reactivity in male rats from two psychogenetically selected lines. *J Neuroendocrinol*. 1997;9:169-175.
29. Perrez M, Reichert M. *Stress, Coping, and Health*. Seattle, Wash: Hogrefe & Huber Publishers; 1992.
30. Van Egeren L. Stress and coping and behavioral organization. *Psychosom Med*. 2000;62:451-460.
31. Pavlov I. *Oeuvres choisies*. Moscow, Russia: Editions en langues étrangères; 1954:250-251.
32. Cosnier J. *Les névroses expérimentales*. Paris, France: Editions du Seuil; 1966.
33. Gottesman II. *Schizophrenia Genesis: The Origins of Madness*. New York, NY: WH Freeman and Co; 1991.
34. Goldsmith HH, Lemery KS. Linking temperamental fearfulness and anxiety symptoms: a behavior–genetic perspective. *Biol Psychiatry*. 2000;48:1199-1209.
35. Kandel ER. From metapsychology to molecular biology: explorations into the nature of anxiety. *Am J Psychiatry*. 1983;140:1277-1293.
36. Lister RG. Ethologically based animal models of anxiety disorders. *Pharmacol Ther*. 1990;46:321-340.
37. Shekhar A, McCann UD, Meaney MJ, et al. Summary of a National Institute of Mental Health workshop: developing animal models of anxiety disorders. *Psychopharmacology (Berl)*. 2001;157:327-339.
38. Belzung C, Griebel G. Measuring normal and pathological anxiety-like behaviour in mice: a review. *Behav Brain Res*. 2001;125:141-149.
39. Tarantino ML, Bucan M. Dissection of behavior and psychiatric disorders using the mouse as a model. *Hum Mol Genet*. 2000;9:953-965.
40. Crawley JN. Behavioral phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioral tests. *Brain Res*. 2002;855:18-26.
41. Panksepp J. The sources of fear and anxiety in the brain. In: Panksepp J, ed. *Affective Neuroscience*. New York, NY: Oxford University Press; 1998:206-222.
42. Coplan JD, Rosenblum LA, Gorman JM. Primate models of anxiety. Longitudinal perspectives. *Psychiatr Clin North Am*. 1995;18:727-743.
43. LeDoux J. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000;23:155-184.
44. Redmond DE Jr, Huang YH. Current concepts. II. New evidence for a locus coeruleus-norepinephrine connection with anxiety. *Life Sci*. 1979;25:2149-2162.
45. Southwick SM, Bremner JD, Rasmusson A, Morgan CA III, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biol Psychiatry*. 1999;46:1192-1204.
46. Aston-Jones G, Rajkowski J, Cohen J. Role of locus coeruleus in attention and behavioral flexibility. *Biol Psychiatry*. 1999;46:1309-1320.
47. Ziegler DR, Cass WA, Herman JP. Excitatory influence of the locus coeruleus in hypothalamic-pituitary-adrenocortical axis responses to stress. *J Neuroendocrinol*. 1999;11:361-369.
48. Sullivan GM, Coplan JD, Kent JM, Gorman JM. The noradrenergic system in pathological anxiety: a focus on panic with relevance to generalized anxiety and phobias. *Biol Psychiatry*. 1999;46:1205-1218.
49. Gray JA. The structure of the emotions and the limbic system. In: *Physiology, Emotions and Psychosomatic Illness*. Amsterdam, The Netherlands: Elsevier; 1972:87-129.
50. Gray JA. Three fundamental emotion systems. In: Ekman P, Davidson JR, eds. *The Nature of Emotion*. New York, NY: Oxford University Press; 1994:243-247.
51. Gray JA. *The Neuropsychology of Anxiety. An Enquiry into the Functions of the Septo-hippocampal System*. Oxford, UK: Clarendon Press; 1987.
52. Laborit H. Inhibition of action: interdisciplinary approach to its mechanisms and pathophysiology. In: Traue HC, Pennebaker JW, eds. *Emotion, Inhibition and Health*. Seattle, Wash: Hogrefe & Huber Publishers; 1993:57-79.
53. Selye H. *The Stress of Life*. 2nd revised paperback ed. New York, NY: McGraw Hill; 1984.
54. Vianna DML, Landeira-Fernadez J, Brandão ML. Dorsolateral and ventral regions of the periaqueductal gray matter are involved in distinct types of fear. *Neurosci Biobehav Rev*. 2001;25:711-719.
55. Coplan JD, Lydiard RB. Brain circuits in panic disorder. *Biol Psychiatry*. 1998;44:1264-1276.
56. Goddard AW, Charney DS. Toward an integrated neurobiology of panic disorder. *J Clin Psychiatry*. 1997;58(suppl 2):4-11.
57. LeDoux J. Fear and the brain: where have we been, and where are we going? *Biol Psychiatry*. 1998;44:1229-1238.
58. LeDoux J. *The Emotional Brain*. New York, NY: Simon & Schuster; 1998.
59. LeDoux J. The amygdala and emotion: a view through fear. In: Aggleton JP, ed. *The Amygdala*. Oxford, UK: Oxford University Press; 2000:289-310.
60. Maren S. Neurobiology of Pavlovian fear conditioning. *Annu Rev Neurosci*. 2001;24:897-931.
61. Fendt M, Fanselow MS. The neuroanatomical and neurochemical basis of conditioned fear. *Neurosci Biobehav Rev*. 1999;23:743-760.
62. Phelps EA, O'Connor KJ, Gatenby JC, Gore JC, Grillon C, Davis M. Activation of the left amygdala to a cognitive representation of fear. *Nat Neurosci*. 2002;4:437-441.
63. Killgore WDS, Yurgelun-Todd DA. Sex differences in amygdala activation during the perception of facial affect. *Neuroreport*. 2001;12:2543-2547.
64. Davis M. The role of the amygdala in conditioned and unconditioned fear and anxiety. In: Aggleton JP, ed. *The Amygdala*. Oxford, UK: Oxford University Press; 2000:213-287.
65. Holahan MR, White NM. Conditioned memory modulation, freezing, and avoidance as measures of amygdala-mediated conditioned fear. *Neurobiol Learn Mem*. 2002;77:250-275.
66. Killcross S, Robbins TW, Everitt BJ. Different types of fear-conditioned behaviour mediated by separate nuclei within the amygdala. *Nature*. 1997;388:377-380.
67. Goldstein LE, Rasmusson AM, Bunney BS, Roth RH. Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. *J Neurosci*. 1996;16:4787-4798.
68. Holland PC, Gallagher M. Amygdala circuitry in attentional and representational processes. *Trends Cogn Sci*. 1999;3:65-73.
69. Garavan H, Pendergrass JC, Ross TJ, Stein EA, Risinger RC. Amygdala response to both positively and negatively valenced stimuli. *Neuroreport*. 2001;12:2779-2783.

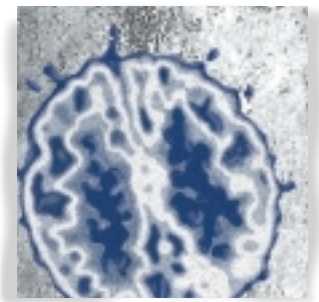
70. Amaral DG. The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety. *Biol Psychiatry*. 2002;51:11-17.
71. File S, Gonzalez LE, Gallants R. Role of the basolateral nucleus of the amygdala in the formation of a phobia. *Neuropsychopharmacology*. 1998;19:397-405.
72. Davis M, Walker DL, Lee Y. Roles of the amygdala and bed nucleus of the stria terminalis in fear and anxiety measured with the acoustic startle reflex. Possible relevance to PTSD. *Ann N Y Acad Sci*. 1997;821:305-331.
73. Davis M. Are different parts of the extended amygdala involved in fear versus anxiety? *Biol Psychiatry*. 1998;44:1239-1247.
74. Treit D, Pesold C, Rotzinger S. Dissociating the anti-fear effects of septal and amygdaloid lesions using two pharmacologically validated models of rat anxiety. *Behav Neurosci*. 1993;105:770-785.
75. Treit D, Pesold C, Rotzinger S. Noninteractive effects of diazepam and amygdaloid lesions in two animal models of anxiety. *Behav Neurosci*. 1993;107:1099-1105.
76. Kalin NH, Shelton SE, Davidson RJ, Kelley AE. The primate amygdala mediates acute fear but not the behavioral and physiological components of anxious temperament. *J Neurosci*. 2001;21:2067-2074.
77. Aggleton JP. *The Amygdala. A Functional Analysis*. 2nd ed. Oxford, UK: Oxford University Press; 2000.
78. Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci*. 1997;20:78-84.
79. Lopez JF, Akil H, Watson SJ. Neural circuits mediating stress. *Biol Psychiatry*. 1999;46:1461-1471.
80. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci*. 1999;3:11-21.
81. Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdala. *Biol Psychiatry*. 2002;51:68-80.
82. Gainotti G, Caltagirone C. *Emotions and the Dual Brain*. Berlin, Germany: Springer-Verlag; 1989.
83. Sullivan RM, Gratton A. Behavioral effects of excitotoxic lesions of ventral medial prefrontal cortex in the rat are hemisphere-dependent. *Brain Res*. 2002;927:69-79.
84. Tanaka M, Yoshida M, Emoto H, Ishii H. Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. *Eur J Pharmacol*. 2000;405:397-406.
85. Shishkina GT, Kalinina TS, Sournina NY, Saharov DG, Kobzev VF, Dygalo NN. Effects of antisense oligodeoxynucleotide to the alpha2A-adrenoceptors on the plasma corticosterone level and on elevated plus-maze behavior in rats. *Psychoneuroendocrinology*. 2002;27:593-601.
86. Schramm NL, McDonald MP, Limbird LE. The α_{2A}-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. *J Neurosci*. 2001;21:4875-4882.
87. Bagdy G. Serotonin, anxiety, and stress hormones. Focus on 5-HT receptor subtypes, species and gender differences. *Ann N Y Acad Sci*. 1998;851:357-363.
88. Graeff FG, Viana MB, Mora PO. Dual role of 5-HT in defense and anxiety. *Neurosci Biobehav Rev*. 1997;21:791-799.
89. Graeff FG, Guimaraes FS, De Andrade TG, Deakin JF. Role of 5-HT in stress, anxiety, and depression. *Pharmacol Biochem Behav*. 1996;54:129-141.
90. Gingrich JA, Hen R. Dissecting the role of the serotonin system in neuropsychiatric disorders using knockout mice. *Psychopharmacology (Berl)*. 2001;155:1-10.
91. Olivier B, Pattij T, Wood SJ, Oosting R, Sarnyai Z, Toth M. The 5-HT(1A) receptor knockout mouse and anxiety. *Behav Pharmacol*. 2001;12:439-450.
92. Pattij T, Groenink L, Hijzen TH, et al. Autonomic changes associated with enhanced anxiety in 5-HT_{1A} receptor knockout mice. *Neuropsychopharmacology*. 2002;27:380.
93. Zhuang X, Gross C, Santarelli L, Compan V, Trillat AC, Hen R. Altered emotional states in knockout mice lacking 5-HT_{1A} or 5-HT_{1B} receptors. *Neuropsychopharmacology*. 1999;21(2, suppl):52S-60S.
94. Murphy DL, Li Q, Engel S, et al. Genetic perspectives on the serotonin transporter. *Brain Res Bull*. 2001;56:487-494.
95. Nutt DJ, Malizia AL. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. *Br J Psychiatry*. 2001;179:390-396.
96. Möhler H, Crestani F, Rudolph U. $GABA_A$-receptor subtypes: a new pharmacology. *Curr Opin Pharmacol*. 2002;1:22-25.
97. Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300:2-8.
98. Rudolph U, Crestani F, Möhler H. $GABA_A$ receptors subtypes: dissecting their pharmacological functions. *Trends Pharmacol Sci*. 2001;22:188-194.
99. Löw K, Crestani F, Keist R, et al. Molecular and neuronal substrate for the selective attenuation of anxiety. *Science*. 2000;290:131-134.
100. Crestani F, Lorez M, Baer K, et al. Decreased $GABA_A$-receptor clustering results in enhanced anxiety and a bias for threat cues. *Nat Neurosci*. 1999;2:833-839.
101. Bailey DJ, Tezlaff JE, Cook JM, He X, Helmstetter FJ. Effects of hippocampal injections of a novel ligand selective for the $\alpha5\beta2\gamma2$ subunits of the GABA/benzodiazepine receptor on Pavlovian conditioning. *Neurobiol Learn Mem*. 2002;78:1-10.
102. Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. *Front Neuroendocrinol*. 2002;21:1-56.
103. Rupprecht R, di Michele F, Hermann B, et al. Neuroactive steroids: molecular mechanisms of action and implications for neuropsychopharmacology. *Brain Res Brain Res Rev*. 2001;37:59-67.
104. Majewska MD. Steroids and brain activity. Essential dialogue between body and mind. *Biochem Pharmacol*. 1987;36:3781-3788.
105. Costa E, Cheney DL, Grayson DR, et al. Pharmacology of neurosteroid biosynthesis. Role of the mitochondrial DBI receptor (MDR) complex. *Ann N Y Acad Sci*. 1994;746:223-242.
106. Costa E, Auta J, Guidotti A, Korneyev A, Romeo E. The pharmacology of neurosteroidogenesis. *J Steroid Biochem Mol Biol*. 1994;49:385-389.
107. Dunn AJ, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res Brain Res Rev*. 1990;15:71-100.
108. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. *J Endocrinol*. 1999;160:1-12.
109. Smagin GN, Heinrichs SC, Dunn AJ. The role of CRH in behavioral responses to stress. *Peptides*. 2001;22:713-724.
110. Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. *Psychoneuroendocrinology*. 1998;23:219-243.
111. Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiatry*. 1999;46:1167-1180.
112. Heinrichs SC, Joppa M. Dissociation of arousal-like from anxiogenic-like actions of brain corticotropin-releasing factor receptor ligands in rats. *Behav Brain Res*. 2001;122:43-50.
113. Stenzel-Poore MP, Heinrichs SC, Rivest S, Koob GF, Vale WW. Overproduction of corticotropin-releasing factor in transgenic mice: a genetic model of anxiogenic behavior. *J Neurosci*. 1994;14:2579-2584.
114. Bakshi VP, Kalin NH. Corticotropin-releasing hormone and animal models of anxiety: gene–environment interactions. *Biol Psychiatry*. 2000;48:1175-1198.
115. Coste SC, Murray SE, Stenzel-Poore MP. Animal models of CRH excess and CRH receptor deficiency display altered adaptations to stress. *Peptides*. 2001;22:733-741.
116. van Gaalen MM, Reul JHM, Gesing A, Stenzel-Poore M, Holsboer F, Steckler T. Mice overexpressing CRH show reduced responsiveness in plasma corticosterone after a 5-HT_{1A} receptor challenge. *Genes Brain Behav*. 2002;1:174-177.
117. Dirks A, Groenink L, Schipholt MI, et al. Reduced startle reactivity and plasticity in transgenic mice overexpressing corticotropin-releasing hormone. *Biol Psychiatry*. 2002;51:583-590.
118. Muglia LJ, Jacobson L, Weninger SC, Karalis KP, Jeong K, Majzoub JA. The physiology of corticotropin-releasing hormone deficiency in mice. *Peptides*. 2001;22:725-731.
119. Dunn AJ, Swiergiel AH. Behavioral responses to stress are intact in CRF-deficient mice. *Brain Res*. 1999;845:14-20.
120. Weninger SC, Dunn AJ, Muglia LJ, et al. Stress-induced behaviors require the corticotropin-releasing hormone (CRH) receptor, but not CRH. *Proc Natl Acad Sci U S A*. 1999;96:8283-8288.

121. Steckler T, Holsboer F. Corticotropin-releasing hormone receptor subtypes and emotion. *Biol Psychiatry*. 1999;46:1480-1508.
122. Holmes A. Targeted gene mutation approaches to the study of anxiety-like behavior in mice. *Neurosci Biobehav Rev*. 2001;25:261-273.
123. Takahashi LK. Role of CRF1 and CRF2 receptors in fear and anxiety. *Neurosci Biobehav Rev*. 2002;25:627-636.
124. Reul JM, Holsboer F. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Curr Opin Pharmacol*. 2002;2:23-33.
125. Smith GW, Aubry JM, Dellu F, et al. Corticotropin-releasing factor 1–deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. *Neuron*. 1998;20:1093-1102.
126. Kishimoto T, Radulovic J, Radulovic M, et al. Deletion of Crhr2 reveals an anxiolytic role for corticotropin-releasing hormone recptor-2. *Nat Genet*. 2000;24:415-419.
127. Bale TL, Picetti R, Contarino A, Koob GF, Vale WW, Lee KF. Mice deficient for both corticotropin-releasing factor receptor 1 (CRFR1) and CRFR2 have an impaired stress response and display sexually dichotomous anxiety-like behavior. *J Neurosci*. 2002;22:193-199.
128. Kemp CF, Woods RJ, Lowry PJ. The corticotropin-releasing factor–binding protein: an act of several parts. *Peptides*. 1998;19:1119-1128.
129. Seasholtz AF, Burrows HL, Karolyi IJ, Camper SA. Mouse models of altered CRH-binding protein expression. *Peptides*. 2001;22:743-751.
130. Sapolsky RM, Krey LC, McEwen BS. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. *Proc Natl Acad Sci U S A*. 1984;81:6174-6177.
131. Liberzon I, López JF, Flagel SB, Vázquez DM, Young EA. Differential regulation of hippocampal glucocorticoid receptors mRNA and fast feedback: relevance to post-traumatic stress disorder. *J Neuroendocrinol*. 1999;11:11-17.
132. Korte SM. Corticosteroids in relation to fear, anxiety and psychopathology. *Neurosci Biobehav Rev*. 2001;25:117-142.
133. Gass P, Reichardt HM, Strekalova T, Henn F, Tronche F. Mice with targeted mutations of glucocorticoid and mineralocorticoid receptors: models for depression and anxiety? *Physiol Behav*. 2001;73:811-825.
134. Griebel G. Is there a future for neuropeptide receptor ligands in the treatment of anxiety disorders? *Pharmacol Ther*. 1999;82:1-61.
135. van Megen HJ, Westenberg HG, den Boer JA, Kahn RS. Cholecystokinin in anxiety. *Eur Neuropsychopharmacol*. 1996;6:263-280.
136. Rehfeld JF. Cholecystokinin and panic disorder—three unsettled questions. *Regul Pept*. 2000;93:79-83.
137. Dauge V, Lena I. CCK in anxiety and cognitive processes. *Neurosci Biobehav Rev*. 1998;22:815-825.
138. De Oliveira RMW, Del Bel EA, Guimarães FS. Effects of excitatory amino acids and nitric oxide on flight behavior elicited from the periaqueductal gray. *Neurosci Biobehav Rev*. 2001;25:679-685.
139. Schulz P, Walker JP, Peyrin L, Soulier V, Curtin F, Steimer T. Lower sex hormones in men during anticipatory stress. *Neuroreport*. 1996;7:3101-3104.
140. Clement Y, Calatayud F, Belzung C. Genetic basis of anxiety-like behaviour: a critical review. *Brain Res Bull*. 2002;57:57-71.
141. Rogers DC, Jones DNC, Nelson PR, et al. Use of SHIRPA and discriminant analysis to characterise marked differences in the behavioural phenotype of six inbred mouse strains. *Behav Brain Res*. 1999;105:207-217.
142. van Gaalen MM, Steckler T. Behavioural analysis of four mouse strains in an anxiety test battery. *Behav Brain Res*. 2000;115:95-106.
143. Avgustinovich DF, Lipina TV, Bondar NP, Alekseyenko OV, Kudryavtseva NN. Features of genetically defined anxiety in mice. *Behav Genet*. 2000;30:101-109.
144. Bert B, Fink H, Huston JP, Voits M. Fisher 344 and Wistar rats differ in anxiety and habituation but not in water maze performance. *Neurobiol Learn Mem*. 2002;78:11-22.
145. Rex A, Sondern U, Voigt JP, Franck S, Fink H. Strain differences in fear-motivated behavior of rats. *Pharmacol Biochem Behav*. 1996;54:107-111.
146. Wehner JM, Radcliffe RA, Bowers BJ. Quantitative genetics and mouse behavior. *Annu Rev Neurosci*. 2001;24:845-867.
147. Griebel G, Belzung C, Perrault G, Sanger DJ. Differences in anxiety-related behaviours and in sensitivity to diazepam in inbred and outbred strains of mice. *Psychopharmacology (Berl)*. 2000;148:164-170.
148. Garrett KM, Niekrasz I, Haque D, Parker KM, Seale TW. Genotypic differences between C57BL/6 and A inbred mice in anxiolytic and sedative actions of diazepam. *Behav Genet*. 1998;28:125-136.
149. Wigger A, Loerscher P, Weissenbacher P, Holsboer F, Landgraf R. Cross-fostering and cross-breeding of HAB and LAB rats: a genetic rat model of anxiety. *Behav Genet*. 2001;31:371-382.
150. Plomin R, DeFries JC, McClearn GE, McGuffin P. *Behavioral Genetics*. 4th ed. New York, NY: Worth Publishers; 2000.
151. Wehner JM, Radcliffe RA, Rosman ST, et al. Quantitative trait locus analysis of contextual fear conditioning in mice. *Nat Genet*. 1997;17:331-334.
152. Turri MG, Datta SR, DeFries J, Henderson ND, Flint J. QTL analysis identifies multiple behavioral dimensions in ethological tests of anxiety in laboratory mice. *Curr Biol*. 2001;11:725-734.
153. Fernandez-Teruel A, Escorihuela RM, Gray JA, et al. A quantitative trait locus influencing anxiety in the laboratory rat. *Genome Res*. 2002;12:618-626.
154. Escorihuela RM, Fernandez-Teruel A, Gil L, Aguilar R, Tobeña A, Driscoll P. Inbred Roman high- and low-avoidance rats: differences in anxiety, novelty-seeking, and shuttlebox behaviors. *Physiol Behav*. 1999;67:19-26.
155. Steimer T, la Fleur S, Schulz PE. Neuroendocrine correlates of emotional reactivity and coping in male rats from the Roman high (RHA/Verh) and low (RLA/Verh)-avoidance lines. *Behav Genet*. 1997;27:503-511.
156. Roozendaal B, Wiersma A, Driscoll P, Koolhaas JM, Bohus B. Vasopressinergic modulation of stress responses in the central amygdala of the Roman high-avoidance and low-avoidance rat. *Brain Res*. 1992;596:35-40.
157. Wiersma A, Knoellema S, Konsman JP, Bohus B, Koolhaas JM. Corticotropin-releasing hormone modulation of a conditioned stress response in the central amygdala of Roman high (RHA/Verh)-avoidance and low (RLA/Verh)-avoidance rats. *Behav Genet*. 1997;27:547-555.
158. Corda MG, Lecca D, Piras G, Di Chiara G, Giorgi O. Biochemical parameters of dopaminergic and GABAergic neurotransmission in the CNS of Roman high-avoidance and Roman low-avoidance rats. *Behav Genet*. 1997;27:527-536.
159. Aubry JM, Bartanusz V, Driscoll P, Schulz P, Steimer T, Kiss JZ. Corticotropin-releasing factor and vasopressin mRNA levels in Roman high- and low-avoidance rats: response to open field exposure. *Neuroendocrinology*. 1995;61:89-97.
160. Charnay Y, Steimer T, Hugenin C, Driscoll P. [^{3}H]Paroxetine binding sites: brain regional differences between two psychogenetically selected lines of rats. *Neurosci Res Commun*. 1995;16:29-35.
161. Liebsch G, Linthorst ACE, Neumann ID, Reul J, Holsboer FLR. Behavioral, physiological, and neuroendocrine stress responses and differential sensitivity to diazepam in two Wistar rat lines selectively bred for high- and low-anxiety–related behavior. *Neuropsychopharmacology*. 1998;19:381-396.
162. Liebsch G, Montkowski A, Holsboer F, Landgraf R. Behavioural profiles of two Wistar rat lines selectively bred for high or low anxiety-related behaviour. *Behav Brain Res*. 1998;94:301-310.
163. Landgraf R, Wigger A, Holsboer F, Neumann ID. Hyper-reactive hypothalamo-pituitary-adrenocortical axis in rats bred for high anxiety-related behaviour. *J Neuroendocrinol*. 1999;11:405-407.
164. Henniger MSH, Ohl F, Hölter SM, et al. Unconditioned anxiety and social behavior in two rat lines selectively bred for high and low anxiety-related behaviour. *Behav Brain Res*. 2000;111:153-163.
165. Hermann B, Landgraf R, Keck ME, et al. Pharmacological characterisation of cortical γ-aminobutyric acid type A ($GABA_A$) receptor in two Wistar rat lines selectively bred for high and low anxiety–related behaviour. *World J Biol Psychiatry*. 2000;1:137-143.
166. Keck ME, Wigger A, Welt T, et al. Vasopressin mediates the response of the combined dexamethasone/CRH test in hyper-anxious rats: implications for the pathogenesis of affective disorders. *Neuropsychopharmacology*. 2002;26:94-105.
167. Henniger MSH, Spanagel R, Wigger A, Landgraf R, Hölter SM. Alcohol self-administration in two rat lines selectively bred for extremes in anxiety-related behavior. *Neuropsychopharmacology*. 2002;26:729-736.
168. Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev Psychopathol*. 2001;13:419-449.

169. Heim C, Nemeroff CB. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry*. 1999;46:1509-1522.
170. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry*. 2001;49:1023-1039.
171. Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Prog Neurobiol*. 2001;65:427-451.
172. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci*. 2001;24:1161-1192.
173. Wakshlak A, Weinstock M. Neonatal handling reverses behavioral abnormalities induced in rats by prenatal stress. *Physiol Behav*. 1990;48:289-292.
174. Meaney MJ, Mitchell JB, Aitken DH, et al. The effects of neonatal handling on the development of the adrenocortical response to stress: implications for neuropathology and cognitive deficits in later life. *Psychoneuroendocrinology*. 1991;16:85-103.
175. Plotsky PM, Meaney MJ. Early, post-natal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Mol Brain Res*. 1993;18:195-200.
176. Smythe JW, Rowe WB, Meaney MJ. Neonatal handling alters serotonin (5-HT) turnover and 5-HT_2 receptor binding in selected brain regions: relationship to the handling effect on glucocorticoid receptor expression. *Brain Res Dev Brain Res*. 1994;80:183-189.
177. Tejedor-Real P, Costela C, Gibert-Rahola J. Neonatal handling reduces emotional reactivity and susceptibility to learned helplessness. Involvement of catecholaminergic systems. *Life Sci*. 1998;62:37-50.
178. Weizman R, Lehman J, Leschiner S, et al. Long-lasting effect of early-handling on the peripheral benzodiazepine receptor. *Pharmacol Biochem Behav*. 1999;64:725-729.
179. Papaioannou A, Gerozissis K, Prokopiou A, Bolaris S, Stylianopoulou F. Sex differences in the effects of neonatal handling on the animal's response to stress and the vulnerability for depressive behaviour. *Behav Brain Res*. 2002;129:131-139.
180. Beane ML, Cole MA, Spencer RL, Rudy JW. Neonatal handling enhances contextual fear conditioning and alter corticosterone stress responses in young rats. *Horm Behav*. 2002;41:33-40.
181. Fernandez-Teruel A, Escorihuela RM, Driscoll P, Tobena A, Bättig K. Infantile (handling) stimulation and behavior in young Roman high- and low-avoidance rats. *Physiol Behav*. 1991;50:563-565.
182. Fernandez-Teruel A, Escorihuela RM, Castellano B, Gonzàlez B, Tobena A. Neonatal handling and environmental enrichment effects on emotionality, novelty/reward seeking, and age-related cognitive and hippocampal impairments: focus on the Roman rat lines. *Behav Genet*. 1997;6:513-526.
183. Steimer T, Escorihuela RM, Fernandez-Teruel A, Driscoll P. Long-term behavioural and neuroendocrine changes in Roman high-(RHA/Verh) and low-(RLA/Verh) avoidance rats following neonatal handling. *Int J Dev Neurosci*. 1998;16:165-174.

Are there anxious genes?

Deborah J. Morris-Rosendahl, PhD



Anxiety comprises many clinical descriptions and phenotypes. A genetic predisposition to anxiety is undoubted; however, the nature and extent of that contribution is still unclear. Methods for the genetic analysis of such complex disorders is briefly reviewed, followed by a discussion of the comorbidity of anxiety with other psychiatric disorders and their possible common genetic etiology. Extensive genetic studies of the serotonin (5-hydroxytryptamine, 5-HT) transporter (5-HTT) gene have revealed how variation in gene expression can be correlated with anxiety phenotypes. Complete genome-wide linkage scans for panic disorder (PD) susceptibility genes have suggested a locus on chromosome arm 7p, and association studies have highlighted many candidate genes. A highly significant association between phobias, panic disorder, and a duplication at chromosomal region 15q24-26 is one of the most exciting findings to date. Emerging molecular genetic technologies and the use of increasingly sophisticated animal models of anxiety provide great promise for the future of the field.

Dialogues Clin Neurosci. 2002;4:251-260.

Anxiety is part of the normal human experience. We may speculate that it served human survival during evolution by enhancing preparedness and alertness. However, anxious manifestations are abnormal when they are exaggerated in excess of any objective danger that the individual is facing, when they induce psychological distress or physical ailments, or when they are self-aggravating in a vicious circle. As a subject of clinical diagnosis, anxiety may be chronic, for instance, in some types of personality disorder or in generalized anxiety disorder (GAD); in such cases, it is akin to a "trait." In other instances, anxiety is a short-lived, noncontinuous, discrete symptom, for example, in panic disorder (PD) or in acute stress; then it is a "state," rather than a trait. Anxiety comprises many phenotypes and clinical descriptions. It is routinely partitioned into disorders of general anxiety, panic, phobia, and in some classifications, obsessive-compulsive disorder (OCD); and the lifetime prevalence for the group of disorders has been estimated to be as high as 25%.[1] Even this classification does not go far to encompass the complexity of anxiety, and hence the arduousness of the task of getting at its biological root. The success to date has not been overwhelming; however, some recent studies have provided more hope than was in the past thought to be realistic. OCD is sometimes classified with anxiety (eg, in the *Diagnostic and Statistical Manual of Mental Disorders* [*DSM*]) and sometimes not (eg, in the *International Statistical Classification of Diseases, 10th Revision* [*ICD-10*]). Attempts to unravel the genetics of OCD are numerous and would be best served in a treatise of their own, and so will not be included in this review. Since many genetic studies on anxiety have been performed

Keywords: *anxiety, anxiety disorders, panic disorder, genetics*

Author affiliations: Institute for Human Genetics and Anthropology, Albert Ludwigs University of Freiburg, Freiburg, Germany

Address for correspondence: Deborah J. Morris-Rosendahl, PhD, Institut für Humangenetik und Anthropologie, Albert Ludwigs Universität Freiburg, Breisacherstr 33, D-79106 Freiburg, Germany
(e-mail: morrisro@ukl.uni-freiburg.de)

Selected abbreviations and acronyms

AR	*adenosine receptor*
DZ	*dizygotic*
GAD	*generalized anxiety disorder*
5-HT	*5-hydroxytryptamine (serotonin)*
5-HTT	*5-hydroxytryptamine transporter*
MZ	*monozygotic*
PD	*panic disorder*

on PD and, possibly as a direct result thereof, the most enlightening results to date have been found for PD, a proportionate amount of this review will concentrate on the findings in PD. The aim of this review is by no means to overstate the role of genetics in anxiety, rather to highlight the evidence that exists for the role of genetics in anxiety.

The term "complex trait" has been coined by geneticists to refer to any phenotype that does not exhibit classic mendelian recessive or dominant inheritance attributable to a single gene.[2] In general, complexities arise when the simple correspondence between genotype and phenotype breaks down, because either the same genotype can result in different phenotypes (due to the effects of chance, incomplete penetrance, environment, or interactions with other genes), or different genotypes can result in the same phenotype (eg, phenocopies, due to environmental or random causes). In fact, most traits of medical relevance, and particularly psychiatric disorders, do not follow simple mendelian inheritance. During the last decade, geneticists have taken up the challenge of the genetic dissection of complex traits.

The usual path taken to the elucidation of the genetic basis of psychiatric and other complex disorders is becoming fairly routine. Before undertaking studies aimed at genetic dissection, particularly at the molecular or DNA level, one would ideally like to infer as much as possible about the genetic basis of the trait on the basis of the pattern of disease incidence in families and populations. Hence, first we need evidence for a genetic component to anxiety. A genetic contribution to psychological traits and psychiatric disorders is not in doubt, but the nature and extent of that contribution is still unclear. Genetic epidemiology has assembled convincing evidence that anxiety and related disorders are influenced by genetic factors and that the genetic component is highly complex. While studies of the patterns of inheritance of personality indicate that various dimensions are likely to be influenced by many genes and quantitative traits, it also documents the significance of environmental factors. As the modes of inheritance of anxiety disorders are complex, it has been concluded that multiple genes of small effect, in interaction with each other and with nongenetic neurodevelopmental events, produce vulnerability to the disorder.

Segregation analysis involves fitting a general model to the inheritance pattern of a trait in pedigrees. The only opportunity to examine the expression of a human trait in a fixed genetic background comes from the study of monozygotic (MZ) twins.[3] The absolute risk to an MZ twin of an affected individual provides a direct estimate of penetrance for a given environment. Twin studies generally compare the similarity between identical (MZ) and fraternal (dizygotic [DZ]) twins. DZ twins share on average only half of their genes, as do normal sibs. A higher correlation between MZ than between DZ twins indicates a genetic influence on the trait under investigation. Twin studies of self-reported symptoms of anxiety, often called negative emotionality or neuroticism, consistently indicate that approximately 50% of the variance can be attributed to genetic factors.[4-6]

Tools of the trade

The methods available for the genetic dissection of complex traits, which will be referred to at various stages throughout this review, are linkage analysis, allele-sharing methods, association studies in human populations, and genetic analysis of large crosses in model organisms such as the mouse. For the purposes of this review, I will briefly summarize the methods; however, more detailed accounts abound in the literature.[2,6,7] Linkage analysis is a form of genetic mapping that is used to find the approximate chromosomal location of a putative gene. Linkage studies are based on the identification of large families with many affected members and one is required to specify a mode of inheritance for the disorder. The inheritance of the disorder in the family is then compared with the allelic inheritance of known sections of DNA known as polymorphic markers. The coinheritance, or linkage, of a particular marker allele with the presence or absence of the disorder allows one to define or narrow down the location of the suspected gene. Thus, linkage analysis allows one to find out where a gene is, without knowing what it is. A gene can then be isolated, based solely on its chromosomal location, without regard to its biochemical function, this being known as "positional cloning."[8]

In allele-sharing methods of analysis, one checks whether or not the inheritance pattern of a chromosomal region is consistent with random mendelian segregation. If not, patients and their affected relatives will inherit identical copies of DNA markers within that chromosomal region more often than expected by chance. Since allele-sharing methods are nonparametric (that is, they assume no model for the inheritance of the trait), they tend to be more robust than linkage analysis, particularly for complex disorders, for which the inheritance pattern is not clear. Association studies are case-control studies based on a comparison of unrelated affected and unaffected individuals from a population. An allele of a gene of interest is said to be associated with the trait if it occurs at a significantly higher frequency among affected compared with control individuals. Familial inheritance patterns are irrelevant to the method, however, the choice of the control group and its match to the patient group is vital to the study. Population associations between a genetic marker and a phenotypic trait can arise either from population stratification (ie, ethnic differences, and hence different allele frequencies between populations) or genetic transmission. A refinement of association studies is to use family trios (a patient and his or her parents) or sibling pairs, in an attempt to eliminate problems of population stratification. Association studies have most been applied to genes or DNA markers linked to genes proposed as candidates for a particular trait. Experimental crosses of mice and rats offer an ideal setting for the genetic dissection of mammalian physiology. With the opportunity to study hundreds of meioses from a single set of parents, the problem of genetic heterogeneity disappears, and far more complex genetic interactions can be probed than would be possible in human families. Animal studies relating to anxiety will be described in more detail in the final section of this review.

One way to undertake genetic studies of psychiatric illness is to find a classification that might relate more directly to the inheritance pattern. The ideal would be to find pedigrees in which the disorder segregates in a strictly mendelian fashion, as a recessive or dominant. Although these families may not be phenotypically typical of the disorder, there would be good chance of finding genetic linkage and the first step towards isolating an abnormal gene. This gene and its product may provide a clue as to the type of pathway or mechanism causing the disorder. Unfortunately, such families are not abundant. An alternative is to find other genetically determined features that predispose to psychiatric illness, for example, the deletion of chromosomal region 22q11 has been shown to be associated with an increased risk of developing a psychotic illness.[9] The recent findings of the duplication of part of chromosome 15 in patients with anxiety disorders,[10] described later in this review, has caused great excitement and hope for workers in the field.

Comorbidity of anxiety with other psychiatric disorders

The comorbidity of anxiety disorders with each other and with other psychiatric disorders,[11] particularly mood,[12] has been observed and accepted for many decades. It is known that patients with major depression invariably show either syndromal comorbidity of one or another anxiety disorder or clinically significant severity of anxiety symptoms.[13] Also, the efficacy of many major psychotropic drugs in the treatment of depression and a broad spectrum of anxiety disorders, eg, GAD, PD, social anxiety disorder, and posttraumatic stress disorder (PTSD), is well established. However, wherever possible, mood and anxiety have been separated and delineated into different disorders.

Evidence for a common genetic etiology for bipolar disorder and PD came from a family study[14] in which an unusually high prevalence of PD in 57 families with high rates of bipolar disorder was reported. Families at high risk of PD showed linkage to markers on the long arm of chromosome 18 (18q), whereas families of probands without PD did not. This led the authors to conclude that there may be a genetic subset of patients with bipolar disorder who had comorbid PD. These results were very recently extended and confirmed by the same group in an independent group of bipolar disorder families.[15] In the same recent issue of the *American Journal of Psychiatry*, Rotondo and colleagues[16] conducted a case-control association study of the genetic polymorphisms of three monoamine neurotransmitter system candidate genes, catechol-*O*-methyltransferase (COMT), serotonin (5-hydroxytryptamine or 5-HT) transporter (5-HTT), and tryptophan hydroxylase (TPH), in patients with bipolar disorder with and without lifetime PD. Remarkably, the patients with bipolar disorder without PD showed significantly higher frequencies of the COMT *Met158* and the short *5-HTTLPR* alleles and

genotypes. These results suggest that bipolar disorder with and without comorbid PD represent distinct genetic forms, although no single genetic model could be applied to the subset of families with PD. The boundaries between the bipolar/panic phenotype remain obscure, and the question arises as to whether the bipolar/panic phenotype includes individuals with panic attacks below the threshold for a diagnosis of PD.[15] Thus, it is still not clear whether panic vulnerability in families with a high prevalence of bipolar disorder is the result of general nongenetic activation of anxiety mechanisms, a specific, partially penetrant gene, or a combination of genes.[15]

GAD, which is usually classified under the anxiety spectrum disorders, is defined by excessive and uncontrollable worry about a number of life events or activities for at least 6 months, accompanied by at least three of the following six associated symptoms of negative effect or tension: restlessness, fatigability, concentration difficulties, irritability, muscle tension, and sleep disturbance.[17] Twin and family-based studies have indicated a clear genetic influence in GAD with a heritability of approximately 30%; however, Kendler et al[18,19] found that GAD-associated genetic factors were completely shared with depression, while environmental determinants seemed to be distinct. GAD is associated with high comorbidity rates for other psychiatric disorders, including PD, major depression, dysthymia, social phobia, and specific phobia.[20-24] This notion is consistent with recent models of emotional disorders that view anxiety and mood disorders as sharing common vulnerabilities, but differing on dimensions including, for instance, focus of attention or psychosocial liability.[25]

Anxiety as a behavioral trait

Anxiety-related traits are fundamental, enduring, and continuously distributed dimensions of normal human personality.[26,27] Attempts to dissect out anxiety-related personality traits, including fearfulness, emotional stability, and stress reactivity, and to measure their heritability, are possibly the most difficult and definitely amongst the most contentious. The analysis of genetic contributions to anxiety-related or aggressive behavior is both conceptually and methodologically difficult, so that consistent findings remain sparse. Mood, anxiety, emotion, and cognition are modulated by the serotonergic midbrain raphe system, and a dysregulation of 5-HTT expression might be important in the course of these disorders.[28] Transporter-facilitated uptake of 5-HT has been implicated in anxiety in human and animal models and is the site of action of widely used uptake-inhibiting antidepressant and antianxiety drugs. The 5-HTT terminates the synaptic actions of 5-HT by sodium-dependent reuptake of 5-HT into the presynaptic vesicles. Heils et al[29] isolated and cloned the 5´-regulatory region of the 5-HTT gene, *SLC6A4*, which is located on chromosomal region 17q12. Systematic screening for length variations and functional promotor analyses revealed a genetic polymorphism that shows allelic variation in transcriptional activity and protein expression.[30] The short variant of the polymorphism reduces the transcriptional efficiency of the 5-HTT gene promotor, resulting in decreased 5-HTT expression and 5-HT uptake in lymphoblasts. Extensive genetic studies of the 5-HTT gene have revealed how variation in gene expression can be correlated with anxiety phenotypes. Association studies in two independent population and family-based samples, totaling 505 individuals, revealed that the 5-HTT polymorphism accounts for 3% to 4% of total variation and 7% to 9% of inherited variance in anxiety-related personality traits in individuals as well as sibships.[31] Using three different personality assessment scales, the results showed that the *5-HTTLPR* influences a constellation of traits related to anxiety. Lesch et al[31] stressed that the associations reported by them represent only a small portion of the genetic contribution to anxiety-related personality traits, and that if other genes were hypothesized to contribute similar gene dosage effects to anxiety, approximately 10 to 15 genes might be predicted to be involved.

Panic disorder

Probably the most genetic studies of anxiety have been conducted on patients with PD. PD typically has its onset between late adolescence and the mid-30s, and is strikingly different from other types of anxiety in that the panic attacks are sudden, appear to be unprovoked, and are often disabling. The first attacks are frequently triggered by physical illnesses, psychosocial stress, or certain drug treatments or drugs of abuse that increase the activity of neural systems involved in fear responses. Panic attacks respond to a variety of antidepressant drugs, they can be precipitated pharmacologically by carbon dioxide (CO_2), caffeine, lactate, cholecystokinin tetrapeptide,[32] and serotonergic compounds[33]; and func-

tional imaging studies have identified neurological correlates of attacks.[34-36] All of these observations speak for a physiological vulnerability. Sensitivity to CO_2 and lactate may indicate a distinct genetic liability.[37-39] Candidate genes for association studies in PD have often been selected on the basis of the molecular mechanisms of drugs utilized in challenge tests, such as *m*-chlorophenylpiperazine (mCPP), a nonselective 5-HT_{2C} receptor agonist.[40] The enhancement of GABAergic (GABA, γ-aminobutyric acid) neurotransmission has been closely linked to antipanic drug efficacy.

Hettema et al[41] recently published the results of meta-analysis of selected epidemiological studies, in order to summarize and quantify the information gathered to date on the familial aggregation of anxiety disorders and the relative contributions of genetics and environment to their etiology. Five family studies of PD, all from clinical populations that met their inclusion criteria, were included in the meta-analysis. All five studies supported the familial aggregation of PD, with a significant association between PD in the probands and PD in first-degree relatives. The unadjusted aggregate risk based on 1356 total first-degree relatives of PD probands was 10%, compared with 2.1% in 1187 comparison relatives. Small twin studies of PD by Torgersen[42,43] have found concordance rates of 22% to 31% for MZ twins and 0% for DZ twins. In an enlarged sample, the same group, using *DSM-III-R* criteria, found concordance rates of 25% for MZ twins and 10% for DZ twins.[44] A large population-based twin study of PD in women found a 24% MZ concordance and 11% DZ concordance using a "narrow clinician's" diagnosis.[45] The estimate of narrow-sense (additive) heritability of PD using this diagnosis was 46%. This is similar to what has been observed for the other anxiety disorders. Interestingly, the subdivision of PD patients according to age of onset before or after 20 years of age led to remarkable differences in risk of 22% and 8%, respectively. This indicates a much stronger genetic component in early-onset PD as opposed to late-onset PD; a finding consistent with other complex disorders, for example, Alzheimer's disease and breast cancer, which are rendered genetically more homogeneous when focusing on early-onset cases.[46,47]

Models for the mode of inheritance of PD remain highly speculative. Some segregation analyses have suggested the involvement of a major gene,[48,49] other studies have provided equal support for both recessive and dominant genetic models.[50,51] Two complete genome-wide linkage scans for PD liability genes have been published.[52,53] Knowles et al[52] genotyped up to 23 families with many affected individuals, with 540 microsatellite DNA markers. Since their previous studies had indicated that a large number of PD cases in the general population are likely to be phenocopies,[50,51] they included phenocopies, reduced penetrance, and "unaffected" individuals in their analysis. Six DNA markers, on chromosomal regions 1, 7, 17, 20p, and 20q (short and long chromosome arms, respectively) and X and Y gave promising lod scores (>1); however, no markers gave lod scores that exceeded the significant threshold of 3.3 suggested for declaring linkage to a complex trait in a genome scan.[7] In the more recent study of Crowe et al,[53] in which they genotyped 23 multiply affected families with a different set of 469 markers, the highest lod score obtained (2.23) was for a marker on the short arm of chromosome 7 (7p15), within the same region (within 10 cM) of one of the markers to which Knowles et al[52] had detected possible linkage. This replication of a previous finding adds importance to the result, and interesting candidate genes in this region have been highlighted. The corticotropin-releasing hormone receptor 2 locus maps between the two markers that showed possible linkage on 7p, and mouse knockouts for this gene have shown increased anxiety-related behaviors.[54] Similarly, the elastin gene is located within the region of possible linkage, and is also of interest because of the prevalence of joint hypermobility in patients with PD, which is discussed in a separate section below.

In addition to the linkage studies in PD, a number of candidate, or putative vulnerability, genes have been assessed in association studies. A role of monoamine neurotransmitters in the etiology of PD has been suggested by the observation that increased serotonergic neurotransmission provokes anxiety even up to the level of panic attacks in PD patients[33] and that decreased 5-HT uptake is found in patients with anxiety disorders.[55] Although it could be hypothesized that enhanced serotonergic neurotransmission in PD is due to increased 5-HT, no association with *5-HTTLPR*-dependent variation in 5-HTT expression and PD was detected in different populations.[56-58] Monoamine oxidase A (MAOA), an enzyme involved in the degradation of 5-HT and norepinephrine and thus positioned at the crossroads of two monoaminergic systems, is another plausible candidate gene.[25] A 30-bp repeat polymorphism was recently identified in the promotor region of the MAOA gene that

differentially modulates gene transcription.[59] Variation in the number of repeats in the MAOA polymorphic region showed allele-dependent transcriptional efficiency, with the effectiveness of the 3-repeat allele being two times less than alleles with longer repeats. An association study in two independent samples of 209 individuals revealed that longer alleles were significantly more frequent in female patients than controls. Considering that the inhibition of MAOA is clinically effective in the treatment of PD, particularly in women, these findings suggest that altered MAOA activity may be a gender-specific risk factor for PD.

Caffeine, an adenosine receptor (AR) antagonist, induces panic attacks in patients with the disorder[60] and caffeine intoxication (*DSM-III-R*) resembles anxiety disorders. Adenosine analogues have depressant effects on respiratory function in the brainstem, and an impairment of depressant brainstem respiratory mechanisms are considered a central feature in PD.[61] These and other observations have led to the hypothesis that the effectiveness of adenosinergic neuromodulation in patients with PD may be impaired due to changes in receptor function. Four different human AR subtypes have thus far been identified, the A_1 and A_{2a} of which mediate the central nervous system effects of adenosine. Deckert et al[62] systematically searched for mutations in the A_1 and A_{2a} genes in patients with PD and, although only silent mutations or polymorphisms were found, a significant association between an A_{2a}AR polymorphism and PD was found. This polymorphism must not be directly involved in the etiology of PD, but may be in linkage disequilibrium with a true functional variant either in this or a nearby gene. Further evidence for involvement of ARs in anxiety has been provided in mouse models. Mice in which the A_{2a} or A_1 receptors had been disrupted or "knocked out" scored higher in anxiety tests, and male $A_{2a}R^{-/-}$ mice (homozygous $A_{2a}R$ knockout mice) were much more aggressive towards intruders.[63,64]

Phobias

Kendler et al[65] investigated the reliability and heritability of unreasonable fears and phobias in a population-based sample of 1942 female twins. Phobia was defined as the presence of a fear that the respondent recognized as unreasonable and that, in the judgment of the interviewer, objectively interfered with the respondent's life. Unreliability occurred both for subject recall of unreasonable fears and for interviewer assessment of which fears constituted phobias. When fears and phobias were examined together in a multiple threshold model, their results suggested that the resemblance between twins was due solely to genetic factors, with estimated total heritabilities, after correction for unreliability, of 43% to 67%, with the latter highest value for agoraphobia. These authors concluded that individual-specific environmental experiences play an important role in the development of phobias, while familial–environmental factors appear to be of little etiological significance. These "phobia-genic" experiences are, apparently, rarely shared with a cotwin.

Only few population-based association and linkage-disequilibrium studies have been conducted for phobias, with few really promising results, which therefore will not be listed in this review. However, very recently, possibly one of the most exciting genetic studies in anxiety to date has been reported by the group of Estivill,[10] who found an association between the duplication of part of chromosomal region 15q24-26 and irrational fears, or phobias. One of the major uncertainties of the study is the phenotypic classification of the patients; the authors apparently lump panic and phobic disorders together and do not include a detailed clinical description of the patients. For this reason, as well as the importance and hope that their findings provide for the field as a whole, the study deserves a section of its own.

The chromosome 15 connection

Among the biological variables studied in PD, joint laxity or joint hypermobility syndrome has yielded particularly interesting results. Joint laxity is a clinical condition characterized by an increased distensibility and hypermobility of joints. It has a female-to-male ratio of 3:1, a dominant pattern of inheritance, and a prevalence of 10% to 15%.[66] Joint laxity is a feature common to several hereditary diseases of the connective tissue, and has also been significantly associated with mitral valve prolapse,[67] but a specific joint laxity gene has not been identified. Strong associations between joint laxity, mitral valve prolapse, and anxiety disorders have been described.[68-71] On the basis of a case-control study in rheumatology patients,[68] it was reported that PD, agoraphobia, and simple phobia were four times more common in patients with joint laxity than in controls.[72] A second case-control study, carried out in psychiatric patients,

found that joint laxity was 16-times more common in patients with panic/agoraphobia than in controls.[73]

Before embarking on a linkage study in seven extended families each with many members affected with panic/phobic disorders and joint laxity, who all came from a small village near Barcelona, Spain, Estivill's group performed a cytogenetic study in 10 patients,[10] in order to exclude chromosomal rearrangements in their patients. A putative alteration on chromosome 15 was identified, consisting of a slight difference in size between the chromosome homologs, together with a different G-banding pattern at 15q24-26 in some metaphases. Further molecular analysis of this chromosome region using fluorescent in situ hybridization (FISH) revealed an interstitial duplication at 15q24-26 (named *DUP25*). FISH analysis of all available samples found the duplication in 72% of patients. They then analyzed the *DUP25* in three control groups and detected it in 6% of samples. The authors then went on to look for the duplication in a set of 70 unrelated patients with phobias and found it in 68 subjects. This degree of association is one of the strongest reported for a psychiatric disorder and a genetic polymorphism. There are, however, many questions that require further clarity, and which additional studies may answer. For example, what is surprising is the broad clinical classification of the anxiety disorders in the patients with the *DUP25*. From the description of the patients, one could assume that there is a common genetic predisposition to all types of phobia, which other studies do not support. The other surprising finding was the complete lack of linkage between the phenotype and DNA markers that flank or are contained within the duplication. Gratacòs et al[10] explain this to be a result of the nonmendelian segregation of the duplication within families, since the segregation of the duplication in families is far from simple. Cases of de novo duplication, reversion from duplicated to nonduplicated chromosomes, and the apparent conversion from one form of the duplication to another were all observed within families. The duplication also exhibits mosaicism, in that it is not present in all cells analyzed. The authors propose that the mechanism by which the 15q24-26 duplication leads to panic and phobic disorders and joint laxity is probably through a dosage effect, with the overexpression of one or several genes present in the duplicated region; however, we will have to await further studies to shed more light on this association.

Animal models of anxiety

A complementary approach to genetic studies of anxiety and related disorders in humans involves the investigation of genes and their protein products implicated in the brain neurocircuitry of fear and anxiety in animal models. Anxiety is one of the psychiatric syndromes best suited to analogy with animal states. It is well understood that fear, escape, or avoidance behavior, and panic-like responses are ubiquitous throughout animal phylogeny, and as Gorman et al[74] have posited, it takes relatively little intuition to recognize that a rodent that avoids entering a cage in which adverse stimulus has been presented in the past, emulates a phobic patient avoiding a situation that has previously elicited a panic attack. However, as the same authors caution,[74] the analogy of panic attacks to animal fear and avoidance responses "is to be sure, imperfect." Most animal models of anxiety states involve conditioning, and it is not at all clear that PD or any other anxiety disorder except PTSD involves prior exposure to any aversive stimulus. Nevertheless, there are many aspects of conditioned fear in animals that make the analogy with human phenotypes (eg, panic attacks) irresistible, and thus validate the pursuit of genetic studies in model animals.

The mouse has long been regarded as an optimal model system for mammalian genetics. High-resolution genetic maps, large sets of highly polymorphic markers, and the availability of inbred strains of genetically identical mice can now be combined with transgenic and gene-targeting technologies that permit the direct manipulation of the mouse genome. The availability of inbred strains eliminates trait variation due to differences in genetic background, and the ability to sample multiple, essentially identical individuals permits assessment of subtle interstrain differences in the expression of complex traits. At the same time, the number of valid and reliable mouse behavioral testing paradigms is rapidly expanding and these can be used to assess many aspects of behavioral capability.

A number of studies have now indicated that quantitative trait loci on specific chromosomes are associated with heightened emotionality and with fear-conditioning in rodents. For example, Flint et al[75] showed that three loci on mouse chromosomes 1, 12, and 15 were associated with decreased activity and increased defecation in a novel environment. They concluded that these loci were responsible for heightened "emotionality" and

speculated that the genetic basis of emotionality is similar in other species, and may underlie the psychological trait of susceptibility to anxiety in humans. In two studies,[76,77] quantitative trait loci on several chromosomes were found to be associated with contextual fear conditioning in rodents, and chromosome 1 was implicated in both studies. The fact that loci on chromosome 1 have been highlighted in three studies working on such different measures of the same trait is encouraging.[78] On the basis of the increasing evidence that genetic variability in expression and function of proteins that regulate brain neurotransmitter systems (eg, receptors, ion channels, transporters, and enzymes) is associated with complex behavioral traits, research is also emphasizing the molecular psychobiological basis of anxiety-related behavior in rodents, and increasingly in nonhuman primates.[25]

Conclusion

Anxiety disorders belong to the category of complex diseases for which intense research efforts are focused on the identification of genetic susceptibility factors. Emerging tools and technologies for genetic analysis will provide the groundwork for an advanced stage of gene identification and functional studies in anxiety and related disorders. More than 1.4 million single nucleotide polymorphisms (SNPs) have been identified in the human genome. This collection should allow the initiation of genome-wide linkage disequilibrium mapping of genes influencing anxiety in the human population.

The duplication of part of chromosome 15 is probably a major genetic factor of susceptibility for panic and phobic disorders, and its identification may have important implications for psychiatry and health. If the findings of Gratacòs et al[10] are confirmed, and the duplication is shown to segregate in a nonmendelian fashion, it then suggests another line of investigation for complex disorders. Large-scale chromosomal rearrangements are common enough in pericentromeric regions for cytogeneticists to ignore size variation as an irrelevant polymorphism; however, in the future they will perhaps be assigned greater importance. Complex repeat regions at the ends of chromosomes also show size variation, involving hundreds of kilobases of DNA, some of which may contain functional genes.[79,80]

What holds great promise for the future is the increasing development of techniques that alter or inactivate gene expression. Whereas in the past, genes could be inactivated (knocked out) from the embryological stage throughout the life span of the animal, conditional mutants allow the regulation of expression of a particular gene by switching it on or off.[81,82] Thus, one can refine experiments to a much greater degree by the timing of the expression of a particular gene. With the achievement of the sequencing of the human genome, and the active development of techniques for large-scale molecular genetic analysis of the genome, there is now hope for the identification of the contribution of particular genes to the development of these disorders. Eventually, the nature of the gene products might provide the clues to novel treatment options. ❑

I am very grateful to Dr Marc-Antoine Crocq for his critical reading of the manuscript and advice.

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of *DSM-III-R* psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51:8-19.
2. Lander ES, Schork NJ. Genetic dissection of complex traits. *Science*. 1994;265:2037.
3. Neale MC, Cardon LR, *Methodology for Genetic Studies of Twins and Families*. Boston, Mass: Kluwer Academic; 1992.
4. Loehlin JC. Partitioning environmental and genetic contributions to behavioral development. *Am Psychol*. 1989;44:1285-1292.
5. Bouchard TJ Jr, Lykken DT, McGue M, Segal NL, Tellegen A. Sources of human psychological differences: the Minnesota Study of Twins reared apart. *Science*. 1990;250:223.
6. Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. *Science*. 1994;264:1733-1739.
7. Lander ES, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet*. 1995;11:241-247.
8. Bender W, Spierer P, Hogness DS. Chromosomal walking and jumping to isolate DNA from the Ace and rosy loci and the bithorax complex in *Drosophila melanogaster*. *J Mol Biol*. 1983;168:17-33.
9. Karayiorgou M, Morris MA, Morrow B, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A*. 1995;92:7612-7616.
10. Gratacòs M, Nadal M, Martín-Santos R, et al. A polymorphic genomic duplication on human chromsome 15 is a susceptibility factor for panic and phobic disorders. *Cell*. 2001;106:367-379.
11. Noyes R Jr, Hoehn-Saric R. *The Anxiety Disorders*. Cambridge, UK: Cambridge University Press; 1998.
12. Maser JD, Cloninger CR, eds. *Comorbidity of Mood and Anxiety Disorders*. Washington, DC: American Psychiatric Press; 1990.
13. Nemeroff CB. Comorbidity of mood and anxiety disorders: the rule, not the exception? *Am J Psychiatry*. 2002;159:3-4.

¿ Hay genes para la ansiedad ?

La ansiedad incluye diversas descripciones clínicas y fenotipos. No cabe duda de que existe una predisposición genética para la ansiedad; sin embargo, aun no está aclarada la naturaleza y el alcance de esta contribución. En este artículo se revisan brevemente los métodos para el análisis genético de estos complejos trastornos y a continuación se discute la comorbilidad de la ansiedad con otros trastornos psiquiátricos y su posible etiología genética común. Existen numerosos estudios genéticos sobre el gen transportador de serotonina (5-hidroxitriptamina, 5-HT) que han revelado cómo la variación en la expresión genética se puede relacionar con los fenotipos de la ansiedad. Completos mapeos a lo largo del genoma de los enlaces de los genes de susceptibilidad para el trastorno de pánico (TP) han sugerido un sitio en el brazo corto del cromosoma 7 (7p) y estudios de asociación han puesto de relieve muchos genes candidato. Uno de los hallazgos más atractivos a la fecha lo constituye la asociación altamente significativa entre fobias, trastorno de pánico y una duplicación en la región cromosómica 15q24-26. Las tecnologías emergentes de genética molecular y el empleo de modelos animales de ansiedad altamente sofisticados prometen un gran futuro en este campo.

Existe-t-il des gènes de l'anxiété ?

L'anxiété comprend un grand nombre de descriptions cliniques et de phénotypes. Une prédisposition génétique à l'anxiété est indéniable, dont la nature et l'ampleur, toutefois, sont encore incertaines. Les méthodes pour l'analyse génétique de ces troubles complexes sont brièvement passées en revue, suivies par une discussion sur la comorbidité de l'anxiété avec d'autres pathologies psychiatriques et leur possible étiologie génétique commune. De vastes études génétiques sur le gène du transporteur (5-HTT) de la sérotonine (5-hydroxytryptamine, 5-HT) ont révélé l'existence d'une corrélation entre les variations de l'expression de ce gène et les phénotypes de l'anxiété. Des explorations complètes de tout le génome à la recherche de liaisons pour les gènes de la sensibilité au trouble panique (TP) ont montré un locus sur le bras du chromosome 7p et des études d'association ont mis en avant de nombreux gènes candidats. Un des faits les plus passionnants à noter a été la découverte d'une association hautement significative entre la phobie, le trouble panique et une duplication de la région chromosomique 15q24-26. Les technologies de génétique moléculaire émergentes et l'utilisation de modèles animaux de l'anxiété de plus en plus sophistiqués permettent les plus grands espoirs pour l'avenir de ce domaine.

14. Mackinnon DF, McMahon FJ, Simpson SG, McInnis MG, DePaulo JR. Panic disorder with familial bipolar disorder. *Biol Psychiatry*. 1997;42:90-95.

15. Mackinnon DF, Zandi PP, Cooper J, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry*. 2002;159:30-35.

16. Rotondo A, Mazzanti C, Dell'Osso L. Catechol *O*-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. *Am J Psychiatry*. 2002;159:23-29.

17. Brown TA. The nature of generalized anxiety disorder and pathological worry: current evidence and conceptual models. *Can J Psychiatry*. 1997;42:817-825.

18. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Arch Gen Psychiatry*. 1992;49:716-722.

19. Kendler KS. Major depression and generalised anxiety disorder. Same genes, (partly) different environments—revisited. *Br J Psychiatry*. 1996;(suppl):68-75.

20. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Generalized anxiety disorder in women. A population-based twin study [see comments]. *Arch Gen Psychiatry*. 1992;49:267-272.

21. Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Arch Gen Psychiatry*. 1995;52:374-383.

22. Roy MA, Neale MC, Pedersen NL, Mathe AA, Kendler KS. A twin study of generalized anxiety disorder and major depression. *Psychol Med*. 1995;25:1037-1049.

23. Skre I, Onstad S, Edvardsen J, Torgersen S, Kringlen E. A family study of anxiety disorders: familial transmission and relationship to mood disorder and psychoactive substance use disorder. *Acta Psychiatr Scand*. 1994;90:366-374.

24. Weissman MM. Family genetic studies of panic disorder. *J Psychiatr Res*. 1993;27:69-78.

25. Lesch KP. Molecular foundation of anxiety disorders. *J Neural Transm*. 2001;108:717-746.

26. Cloninger CR. A unified biosocial theory of personality and its role in the development of anxiety states. *Psychiatr Dev*. 1986;4:167-226.

27. Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry*. 1987;44:573.

28. Lesch KP, Greenberg BD, Bennett A, Higley JD, Murphy DL. Serotonin transporter, personality, and behavior: toward dissection of gene–gene and gene–environment interaction. In: Benjamin J, Ebstein RP, Belmaker RH, eds. *Molecular Genetics and the Human Personality*. Washington, DC: American Psychiatric Press; 2002.

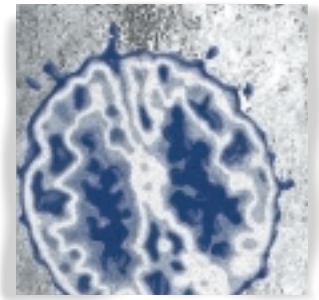
29. Heils A, Teufel A, Petri S, et al. Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. *J Neural Transm Gen Sect*. 1995;102:247-254.

30. Heils A, Teufel A, Petri S, et al. Allelic variation of human serotonin transporter gene expression. *J Neurochem*. 1996;66:2621-2624.

31. Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996;274:1527-1531.
32. Bradwejn J, Koszycki D. Comparison of the panicogenic effect of cholecystokinin 30–33 and carbon dioxide in panic disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 1991;15:237-239.
33. Kahn RS, Wetzler S. *m*-Chlorophenylpiperazine as a probe of serotonin function. *Biol Psychiatry*. 1991;30:1139-1166.
34. Ballenger JC, Davidson JR, Lecrubier Y. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry*. 1998;59(suppl 8):47-54.
35. De Montigny C. Cholecystokinin tetrapeptide induces panic-like attacks in healthy volunteers. Preliminary findings. *Arch Gen Psychiatry*. 1989;46:511-517.
36. Dager SR, Strauss WL, Marro KI, Richards TL, Metzger GD, Artru AA. Proton magnetic resonance spectroscopy investigation of hyperventilation in subjects with panic disorder and comparison subjects. *Am J Psychiatry*. 1995;152:666-672.
37. Balon R, Jordan M, Pohl R, Yeragani VK. Family history of anxiety disorders in control subjects with lactate-induced panic attacks. *Am J Psychiatry*. 1989;146:1304-1306.
38. Perna G, Caldirola D, Arancio C, Bellodi L. Panic attacks: a twin study. *Psychiatry Res*. 1997;66:69-71.
39. Reschke AH, Mannuzza S, Chapman TF, et al. Sodium lactate response and familial risk for panic disorder. *AmJ Psychiatry*. 1995;152:277-279.
40. Deckert J, Meyer J, Catalano M, et al. Novel 5'-regulatory region polymorphisms of the 5-HT_{2c} receptor gene: association study with panic disorder. *Int J Neuropsychopharmacol*. 2000;3:321-325.
41. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry*. 2001;158:1568-1578.
42. Torgersen S. Genetic factors in anxiety disorders. *Arch Gen Psychiatry*. 1983;40:1085-1089.
43. Torgersen S. Comorbidity of major depression and anxiety disorders in twin pairs. *Am J Psychiatry*. 1990;147:1199-1202.
44. Skre I, Torgersen S, Lygren S, Kringlen E. A twin study of *DSM-III-R* anxiety disorders. *Acta Psychiatr Scand*. 1993;88:225-228.
45. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Panic disorder in women: a population-based twin study. *Psychol Med*. 1993;23:397-406.
46. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science*. 1990;250:1684-1689.
47. Clark RF, Goate AM. Molecular genetics of Alzheimer's disease. *Arch Neurol*. 1993;50:1164-1172.
48. Pauls DL, Bucher KD, Crowe RR, Noyes RJ. A genetic study of panic disorder pedigrees. *Am J Hum Genet*. 1980;32:639-644.
49. Crowe RR, Noyes R, Pauls DL, Slymen D. A family study of panic disorder. *Arch Gen Psychiatry*. 1983;40:1065-1069.
50. Vieland VJ, Hodge SE, Lish JD, Adams P, Weissman MM. Segregation analysis of panic disorder. *Psychiatr Genet*. 1993;3:63-71.
51. Vieland VJ, Goodman DW, Chapman T, Fyer AJ. New segregation analysis of panic disorder. *Am J Med Genet*. 1996;67:147-153.
52. Knowles JA, Fyer AJ, Vieland VJ, et al. Results of a genome-wide genetic screen for panic disorder. *Am J Med Genet*. 1998;81:139-147.
53. Crowe RR, Goedken R, Samuelson S, Wilson R, Nelson J, Noyes R Jr. Genomewide survey of panic disorder. *Am J Med Genet*. 2001;105:105-109.
54. Bale TL, Contarino A, Smith GW. Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behavior and are hypersensitive to stress. *Nat Genet.* 2000;24:410-414.
55. Iny LJ, Pecknold J, Suranyi-Cadotte BE, et al. Studies of a neurochemical link between depression, anxiety, and stress from [^{3}H]imipramine and [^{3}H]paroxetine binding on human platelets. *Biol Psychiatry*. 1994;36:281-291.
56. Deckert J, Catalano M, Heils A, et al. Functional promoter polymorphism of the human serotonin transporter: lack of association with panic disorder. *Psychiatr Genet*. 1997;7:45-47.
57. Matsushita S, Muramatsu T, Kimura M, et al. Serotonin transporter gene regulatory region polymorphism and panic disorder [letter]. *Mol Psychiatry* 1997;2:390-392.
58. Hamilton SP, Heiman GA, Haghighi F, et al. Lack of genetic linkage or association between a functional serotonin transporter polymorphism and panic disorder. *Psychiatr Genet*. 1999;9:1-6.
59. Deckert J, Catalano M, Syagailo YV, et al. Excess of high activity monoamine oxdase A gene promoter alleles in female patients with panic disorder. *Hum Mol Genet*. 1999;8:621-624.
60. Boulenger JP, Uhde TW, Wolff EA, Post RM. Increased sensitivity to caffeine in patients with panic disorder: preliminary evidence. *Arch Gen Psychiatry*. 1984;40:1067-1071.
61. Gorman JM, Fyer MR, Goetz R, et al. Ventilatory physiology of patients with panic disorder. *Arch Gen Psychiatry*. 1988;45:31-39.
62. Deckert J, Nothen MM, Franke P, et al. Systematic mutation screening and association study of the A_1 and A_{2a} adenosine receptor genes in panic disorder suggest a contribution of the A_{2a} gene to the development of disease. *Mol Psychiatry*. 1998;3:81-85.
63. Ledent C, Vaugeios JM, Schiffmann SN, et al. Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine A_{2a} receptor. *Nature*. 1997;388:674-678.
64. Johansson B, Halldner L, Dunwiddie TV, et al. Hyperalgesia, anxiety, and decreased hypoxic neuroprotection in mice lacking the adenosine A_1 receptor. *Proc Natl Acad Sci U S A*. 2001;98:9407-9412.
65. Kendler KS, Karkowski LM, Prescott CA. Fears and phobias: reliability and heritability. *Psychol Med*. 1999;29:539-553.
66. Beighton P. *Hypermobility of Joints*. 2nd ed. Berlin, Germany: Springer Verlag; 1989.
67. Pitcher D, Grahame R. Mitral valve prolapse and joint hypermobility: evidence for a systemic connective tissue abnormality? *Ann Rheum Dis*. 1982;41:352-354.
68. Bulbena A, Duró JC, Mateo A, Porta M, Vallejo J. Joint hypermobility syndrome and anxiety disorders. *Lancet*. 1988;2:694.
69. Gorman JM, Goetz RR, Fyer M, et al. The mitral valve prolapse-panic disorder connection. *Psychosom Med*. 1988;50:114-122.
70. Alpert MA, Sabeti M, Kushner MG, et al. Frequency of isolated panic attacks and panic disorder in patients with the mitral valve prolapse syndrome. *Am J Cardiol*. 1992;69:1489-1490.
71. Katerndahl DA. Panic and prolapse: meta-analysis. *J Nerv Ment Dis*. 1993;181:539-544.
72. Bulbena A, Duro JC, Porta M, et al. Anxiety disorders in the joint hypermobility syndrome. *Psychiatry Res*. 1993;46:59-68.
73. Martín-Santos R, Bulbena A, Porta M, Gago J, Molina L, Duró JC. Association between joint hypermobility syndrome and panic disorder. *Am J Psychiatry*. 1998;155:1578-1583.
74. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry*. 2000;157:493-505.
75. Flint J, Corley R, DeFries JC, et al. A simple genetic basis for a complex psychological trait in laboratory mice. *Science*. 1995;269:1432-1435.
76. Wehner JM, Radcliffer RA, Rosmann ST, et al. Quantitative trait locus analysis of contextual fear conditioning in mice. *Nat Genet*. 1997;17:331-334.
77. Caldarone B, Saavedra C, Tartaglia K, Wehner JM, Dudek BC, Flaherty L. Quantitative trait loci analysis affecting contextual conditioning in mice. *Nat Genet*. 1997;17:335-337.
78. Flint J. Freeze! *Nat Genet*. 1997;17:250-251.
79. Wilkie AOM, Higgs DR, Rack KA, et al. Stable length polymorphism of up to 260 kb at the tip of the short arm of human chromosome 16. *Cell*. 1991;64:595-606.
80. Flint J, Bates GP, Clark K, et al. Sequence comparison of human and yeast telomeres identifies structurally distinct subtelomeric domains. *Hum Mol Genet*. 1997;6:1305-1313.
81. Gossen M, Bujard H. Tight control of gene expression in mammalian cells by tetracycline-responsive promotors. *Proc Natl Acad Sci U S A*. 1992;89:5547-5551.
82. Mansuy IM, Bujard H. Tetracycline-regulated gene expression in the brain. *Curr Opin Neurobiol*. 2000;10:593-596.

Pathophysiological aspects of diversity in neuronal inhibition: a new benzodiazepine pharmacology

Hanns Möhler, PhD



Inhibitory interneurons in the brain provide the balance to excitatory signaling. On the basis of brain imaging and human genetics, a deficit in GABAergic inhibition (GABA, γ-aminobutyric acid) has been identified as contributing to the pathophysiology of anxiety disorders, epilepsy, and schizophrenia. Therapeutically, $GABA_A$ receptors play a major role as targets for benzodiazepine drugs. The therapeutic relevance of the multitude of structurally diverse $GABA_A$ receptor subtypes has only recently been identified. α_1-$GABA_A$ receptors were found to mediate sedation, anterograde amnesia, and part of the seizure protection of these drugs, whereas α_2-$GABA_A$ receptors, but not α_3-$GABA_A$ receptors, mediate anxiolysis. Rational drug targeting to specific receptor subtypes has now become possible. Only restricted neuronal networks will be modulated by the upcoming subtype-selective drugs. For instance, anxiolytics devoid of drowsiness and sedation promise more sophisticated interventions in anxiety disorders. A new pharmacology of the benzodiazepine site is on the horizon.

Dialogues Clin Neurosci. 2002;4:261-269.

Keywords: *GABA (γ-aminobutyric acid); $GABA_A$ receptor; neuronal inhibition; anxiety; epilepsy; schizophrenia; benzodiazepine*

Author affiliations: Institute of Pharmacology and Toxicology, University of Zurich and Department of Applied Biosciences, Federal Institute of Technology (ETH) Zurich, Zurich, Switzerland

Inhibitory interneurons in brain function

In the harmonious brain, excitatory and inhibitory synaptic signals coexist in a purposeful balance. However, whereas the neurons that transmit excitatory signals often have rather stereotyped properties, the cells that signal inhibition in the cortex and hippocampus are highly diverse and strikingly different. Inhibitory cells—mostly interneurons because of their often short-range effect—signal to other neurons by liberating, in most cases, the neurotransmitter γ-aminobutyric acid (GABA). Most importantly, the interneurons are built for speed: their action potential is traditionally faster than that of pyramidal cells. Furthermore, the kinetics of synaptic events that excite inhibitory cells are faster than those that excite pyramidal cells.[1,2] The functional result is that pyramidal cell firing is under strict time control to prevent run-away excitation *(Figure 1)*. For instance, in feedforward inhibition, the bisynaptic inhibitory response arrives only 1 to 5 milliseconds after the monosynaptic excitatory input and thereby limits the time window for the summation of excitatory inputs to generate an action potential.[3] In addition to feedforward inhibition, there is feedback inhibition, the output-regulated breaking system for pyramidal cell firing. The firing of a pyramidal cell activates the inhibitory interneuron, which, in turn, inhibits the pyramidal cell. Once the feedback inhibition decays, the principal cell is able to fire again and initiates another cycle of inhibition. Thus,

Address for correspondence: Prof H. Möhler, Institute of Pharmacology and Toxicology, University of Zurich and Department of Applied Biosciences, Federal Institute of Technology (ETH) Zurich, Winterthurerstr 190, CH-8057 Zurich, Switzerland
(e-mail: mohler@pharma.unizh.ch)

this type of inhibitory feedback circuit represents the most simple network for generating a neuronal oscillation *(Figure 1)*. Spontaneous activity in the nervous system often takes the form of rhythms of different frequencies, which underlines the functional relevance of inhibitory interneurons.[4]

Different patterns of rhythmic activity, including theta (4 to 12 Hz), gamma (30 to 100 Hz), and fast (>200 Hz) oscillations, which involve the synchronous firing of principal neurons and interneurons, subserve many functions in the developing and adult central nervous system (CNS). Cortical interneuron networks may generate both slow and fast cortical oscillatory activity.[5-10] Similarly, inhibitory neurons of the thalamic reticular and perigeniculate nuclei generate the synchronized activity of thalamocortical networks.[11] Gamma oscillations (30 to 100 Hz) occur in various brain structures[12,13] and can do so over large distances. They could, therefore, provide a substrate for "binding" together spatially separate areas of cortex, a hypothetical process whereby disparate aspects of a complex object, for example, are combined to form a unitary perception of it.[12,14]

Pathophysiology of neuronal inhibition

If the balance between excitatory and inhibitory activity is shifted pharmacologically in favor of GABA, then anxiolysis, sedation, amnesia, and ataxia arise. On the other hand, an attenuation of the GABAergic system results in arousal, anxiety, restlessness, insomnia, exaggerated reactivity, and even seizures. These pharmacological manifestations point to the contribution of inhibitory neurotransmission to the pathophysiology of brain disorders. A GABAergic deficit is particularly apparent in anxiety disorders, epilepsy, and schizophrenia.

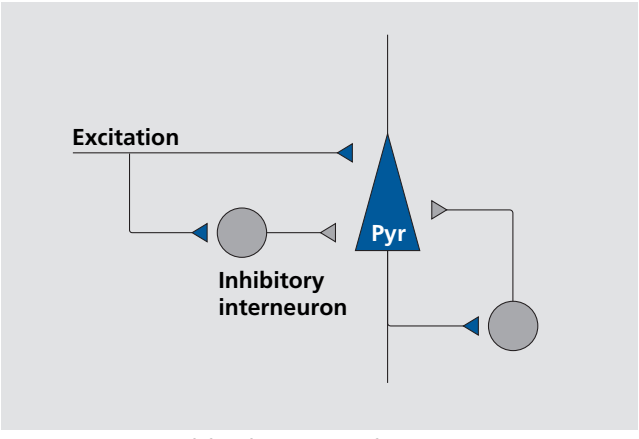


Figure 1. Scheme of feedforward and feedback inhibition through GABAergic interneurons. Pyr, pyramidal cell; GABA, γ-aminobutyric acid.

Anxiety disorders

Anxiety disorders have a high prevalence and are the most common cause of medical intervention in primary care.[15] The pharmacology of the GABA system supports the view that GABAergic dysfunctions are causally related to symptoms of anxiety. For instance, pentylenetetrazole acts by blocking $GABA_A$ receptor function and produces extreme anxiety, traumatic memories, and extreme avoidance behavior when used clinically.[16] Conversely, enhancing GABAergic transmission, eg, by benzodiazepines, is a powerful mechanism to inhibit the experience of anxiety and its aversive reinforcement.

Neuroimaging has given fresh insight into the role of GABAergic inhibition in anxiety disorders. In a recent positron emission tomography (PET) study using ^{11}C-flumazenil, a significant global reduction in flumazenil binding to $GABA_A$ receptors was apparent throughout the brain in patients with panic disorder *(Figure 2)*.[17] The greatest decrease observed occurred in areas thought to be involved in the experience of anxiety, such as the orbitofrontal and temporal cortex. Single photon emission computed tomography (SPECT) studies using the related radioligand ^{123}I-iomazenil have shown similar decreases in binding.[18] A localized reduction in benzodiazepine binding in the temporal lobe has also been reported in generalized anxiety disorders.[19] Furthermore, magnetic resonance spectroscopy has been used to show decreased cortical levels of GABA in patients with panic disorders.[20] These findings are consistent with the view that at least some anxiety disorders are linked to a defective GABAergic neuroinhibitory process.[21]

Anxiety in humans frequently arises at the interface between a genetic predisposition and experience. Recently, the hypothesis that a partial $GABA_A$ receptor deficit would be sufficient to generate an anxiety state was tested. Using molecular biological techniques, the $GABA_A$ receptor deficit seen in patients with anxiety disorders[17] was reproduced in an animal model.[22] The γ_2-subunit of the $GABA_A$ receptor is known to anchor the receptors in the subsynaptic membrane. By reducing the gene dosage for the γ_2-subunit in mice—heterozygosity for the γ_2-subunit gene—the synaptic clustering of

$GABA_A$ receptors was reduced. A partial receptor deficit was apparent throughout most of the brain including the areas that are known to be involved in the processing of anxiety responses, such as the cerebral cortex, amygdala, and hippocampus. The animals behaved normally in a wide range of behavioral tests except when exposed to aversive situations caused by either natural or conditioned fear stimuli. Under such conditions, enhanced anxiety responses and a bias for threat cues were observed.[22] The bias of the animals for threat cues was especially significant since this behavior corresponds to the cognitive deficit contributing to the inability of anxious individuals to distinguish an ambiguous from a threatening situation.[23] Thus, a $GABA_A$ receptor deficit is considered as a predisposition for anxiety disorders in humans. It appears that anxiety symptoms are a sensitive manifestation of an impaired GABAergic neurotransmission.[21,22,24]

Epilepsy

Modification of activity at GABAergic synapses powerfully influences epileptic phenomena. This is a consequence of the role of GABAergic synapses in recurrent inhibitory systems in cortical and other structures, and their effect in limiting the excessive discharge of principal neurons in time and space.

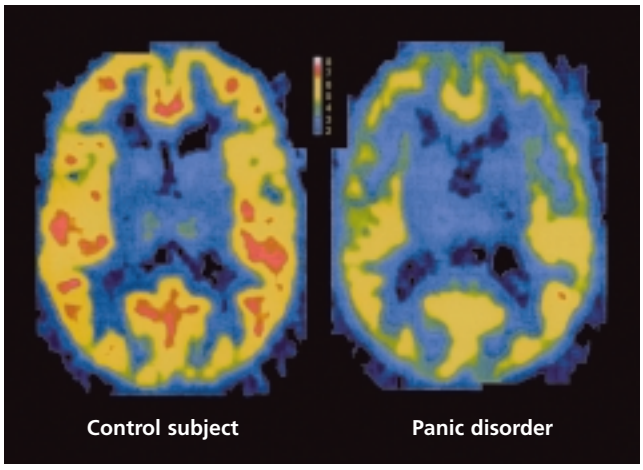


Figure 2. Panic anxiety. Compared with control subjects a reduction in $GABA_A$ receptor binding is apparent in panic disorder by positron emission tomography (PET) imaging with ^{11}C-flumazenil.[17] GABA, γ-aminobutyric acid.
Reproduced from reference 17: Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain $GABA_A$-benzodiazepine receptor binding in panic disorders: preliminary results from a quantitative PET study. *Arch Gen Psychiatry*. 1998;55:715-720. Copyright © 1998, American Medical Association.

Genetic evidence provided the most direct link of epilepsy to $GABA_A$ receptor dysfunction. A K289M mutation located in the extracellular loop of the γ_2-subunit between the transmembrane domain 2 and 3, was linked to familial generalized epilepsy with febrile seizures.[25] At recombinant $GABA_A$ receptors, the K289M mutation reduced the GABA-activated current. Another mutation in the γ_2 subunit of $GABA_A$ receptor was linked to childhood absence epilepsy and febrile seizures with a conserved arginine residue being mutated to glutamine (R43Q).[26] However, since childhood absence epilepsy is not inherited in a simple mendelian manner, the point mutation is not considered to be sufficient by itself to cause this phenotype.
Another example of an altered GABAergic function is that of generalized seizures in infancy related to a pyridoxine deficiency. Since pyridoxal phosphate is a cofactor of glutamic acid decarboxylase, the seizures are related to a deficient synthesis of GABA and can be treated by moderate or high doses of pyridoxine. Furthermore, multiple forms of epilepsy occur in the neurodevelopmental disorder, known as Angelman syndrome, which also shows mental retardation and facial dysmorphism. Genetic studies commonly reveal a major deletion on maternal chromosome 15q11-13[27] with two genes being the major contributors to the syndrome—one is *UBE3A*, encoding a ubiquitin ligase, the other is *GABRB3* encoding the β_2 subunit of $GABA_A$ receptor. Absence epilepsy in man, with a 2- to 3-Hz spike-and-wave discharge in the cortex, is dependent on a thalamocortical loop, which involves several sets of GABAergic synapses in cortex and thalamus. The "waves" correspond to hyperpolarizing activity resulting from synchronous firing of GABAergic neurons.[28] The effects of GABA-related drugs are however complex. Agonists at $GABA_B$ receptors, such as baclofen, exacerbate the spike-and-wave discharges in man and animals; $GABA_B$ antagonists suppress them. Compounds potentiating $GABA_A$ synaptic function commonly exacerbate the discharges, although some benzodiazepines with subtype selective actions can decrease the spike-and-wave discharges. Nevertheless, approximately half the antiepileptic drugs in clinical use are thought to owe their efficacy to either totally or partially potentiating GABAergic inhibitory effects.[29]

Schizophrenia

The neurobiology of schizophrenia has been dominated for the last 30 years by the dopamine hypothesis, although

other transmitter systems are also affected. Alterations in cortical GABAergic systems have been reported in postmortem brain of schizophrenic patients, such as reduced uptake and release of GABA and a reduced activity of glutamic acid decarboxylase. Most conspicuously, the density of axon terminals of GABAergic chandelier neurons was reduced by 40% in the prefrontal cortex.[30] By their axon terminals, chandelier neurons are positioned to powerfully regulate the excitatory output of pyramidal neurons and consequently affect the pattern of neuronal activity in the prefrontal cortex and its projection areas.[30] In addition, altered ratios of subunit splice variants of $GABA_A$ receptors were found in prefrontal cortex of schizophrenics.[31] In addition, benzodiazepine receptor inverse agonists are associated with psychotogenic effects.[32] Furthermore, in primate brain, D_4 dopamine receptors (a member of the D_2 dopamine receptor family with a high affinity for clozapine) modulate GABAergic interneurons in critical brain areas (cerebral cortex, hippocampus, thalamic reticular nucleus, and globus pallidus). Thus, the beneficial effects of clozapine in schizophrenia may be achieved, in part, through D_4-mediated GABA modulation.[33] Finally, GABAergic neurons have been found to be especially vulnerable to glucocorticoid hormones and to glutamatergic excitotoxicity, which may explain the increased number of certain glutamatergic neurons in, for example, the cingulate gyrus of schizophrenic brains and this, in conjunction with a postulated role of stress in the pathogenesis of schizophrenia, would strengthen the assumption of an important role for a GABAergic deficit in schizophrenia.[34] A GABAergic dysfunction that might arise in the course of the disorder may result in long-lasting and perhaps lifelong neuronal sensitivity changes.

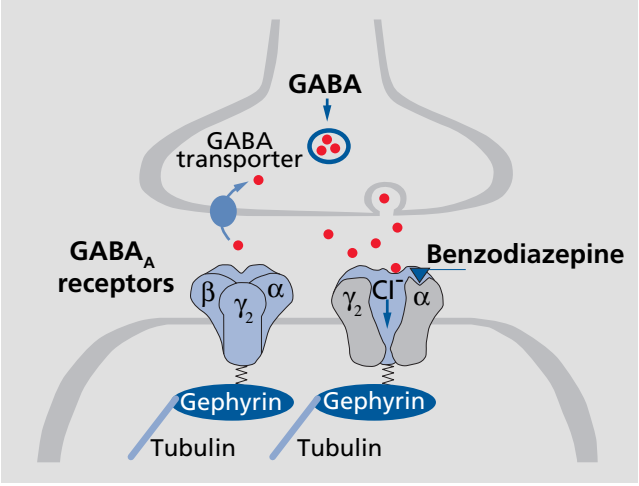


Figure 3. Scheme of a GABAergic synapse depicting the major elements of signal transduction. The ionotropic $GABA_A$ receptors are heteromeric membrane proteins linked in a yet unknown, indirect way to the synaptic anchoring protein gephyrin and the cytoskeleton. GABA, γ-aminobutyric acid.

Modified from reference 35: Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300:2-8. Copyright © 2002, American Society for Pharmacology and Experimental Therapeutics.

Pharmacology of the GABA system

$GABA_A$ receptors are prominent drug targets in that they mediate the action of barbiturates, anesthetics, and neurosteroids and, most importantly, represent the exclusive sites of actions of benzodiazepine drugs, which are in wide clinical use as anxiolytics, hypnotics, and anticonvulsants.[35]

Synaptic action of benzodiazepines

Benzodiazepine drugs modulate $GABA_A$ receptor function in a sophisticated manner that is use-dependent and synapse-specific *(Figure 3)*. Benzodiazepines only become effective at $GABA_A$ receptors that are activated by GABA. In the absence of GABA, the drug remains ineffective (use-dependency). The maximal drug effect varies with the operational configuration of the GABAergic synapse. The number of receptors or the concentration of GABA in the synaptic cleft can differ between synapses. If the release of a single quantum of GABA is able to saturate all the $GABA_A$ receptors, the GABA-induced peak response is not enhanced, or only minimally, in the presence of benzodiazepines. In a synapse that operates under nonsaturating conditions, the drug-induced increase in the affinity of the receptor for GABA results in the recruitment of more receptors for activation by GABA. Thus, benzodiazepine drugs become most strongly effective when the GABAergic operation of the synapse is submaximal.[36,37]

$GABA_A$ receptors and their multiplicity

On the basis of the presence of 7 subunit families comprising at least 18 subunits in the CNS (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, and ρ_{1-3}), the pentameric $GABA_A$ receptors display an extraordinary structural heterogeneity. Most $GABA_A$ receptors subtypes in vivo are believed to be composed of α, β, and γ subunits. The physiological significance of the structural diversity of $GABA_A$ receptors lies in the provision of receptors that differ in their channel kinetics, affinity for GABA, rate of desensitization, and subcellular positioning.[24]

For instance, synaptic and extrasynaptic $GABA_A$ receptors differ kinetically. Extrasynaptic $GABA_A$ receptors containing the δ subunit in dentate gyrus and cerebellum are tailor-made for tonic inhibition, due to their high affinity for GABA and slow desensitization kinetics.[38,39] Marked differences in desensitization kinetics have also been reported for synaptic and extrasynaptic receptors in inferior olivary neurons.[40] Further insights into the heterogeneity of $GABA_A$ receptors is expected to arise from the identification of receptor-associated proteins and their regulation.[41]

Diazepam-sensitive $GABA_A$ receptors

Functionally, $GABA_A$ receptors are best distinguished by their pharmacology. Receptors containing the α_1, α_2, α_3, or α_5 subunits in combination with any of the β subunits and the γ_2 subunit are benzodiazepine sensitive. These receptors represent about 90% of all $GABA_A$ receptors with the major receptor subtype being assembled from the subunits $\alpha_1\beta_2\gamma_2$. Only a few brain regions lack this receptor *(Table I)*.[42-44]

Receptors containing the α_2 or α_3 subunit are less abundant and are highly expressed in brain areas where the α_1 subunit is absent or present at low levels. The α_2 and α_3 subunits are frequently coexpressed with the β_3 and γ_2 subunits, which is particularly evident in hippocampal pyramidal neurons ($\alpha_2\beta_3\gamma_2$) and in cholinergic neurons of the basal forebrain ($\alpha_3\beta_3\gamma_2$) *(Table I)*.

Receptors containing the α_5 subunit are of minor abundance in the whole brain, but are expressed to a significant extent in the hippocampus, where they comprise 15% to 20% of the diazepam-sensitive $GABA_A$ receptor population, predominately coassembled with the β_3 and γ_2 subunits *(Table I)*.

A new benzodiazepine pharmacology

In the search for benzodiazepine site ligands with higher therapeutic selectivity and a reduced side-effect profile, drugs acting at $GABA_A$ receptor subtypes have long been considered to be of potential benefit. However, it was only recently that the pharmacological relevance of $GABA_A$ receptor subtypes was identified based on a genetic approach.[45,46] Mouse lines were generated in which either the α_1-, α_2-, or α_3-$GABA_A$ receptor subtype was diazepam-insensitive. Thus, a deficit in the behavioral response to diazepam was an indication for the role of the respective receptor subtype in wild-type mice.[45,46] This strategy permitted the allocation of the benzodiazepine drug actions to identified $GABA_A$ receptor subtypes *(Figure 4)*.[36,47] In addition, it implicated the neuronal networks expressing the particular receptor in mediating the corresponding drug actions. Experimentally, the benzodiazepine sites were rendered diazepam-insensitive by replacing a conserved histidine residue with an arginine residue in the corresponding α subunit genes (α_1(H101R), α_2(H101R), α_3(H126R), and α_5(H105R)).[45,46]

Composition	Pharmacological characteristics
$\alpha_1\beta_2\gamma_2$	Major subtype (60% of all $GABA_A$ receptors). Mediates the sedative, amnestic, and—to a large extent—anticonvulsant action of benzodiazepine site agonists. High affinity for classical benzodiazepines, zolpidem, and the antagonist flumazenil.
$\alpha_2\beta_3\gamma_2$	Minor subtype (15% to 20%). Mediates anxiolytic action of benzodiazepine site agonists. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem.
$\alpha_3\beta_n\gamma_2$	Minor subtype (10% to 15%). High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem.
$\alpha_4\beta_n\gamma$ / $\alpha_4\beta_n\delta$	Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem.
$\alpha_5\beta_{1/3}\gamma_2$	Less than 5% of all receptors. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Very low affinity for zolpidem.
$\alpha_6\beta_{2,3}\gamma_2$ / $\alpha_6\beta_n\delta$	Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem. Minor population. Lacks benzodiazepine site.
ρ	Homomeric receptors. Insensitive to bicuculline, barbiturates, baclofen, and all benzodiazepine site ligands. Also termed $GABA_C$ receptor. For nomenclature, see reference 44.

Table I. $GABA_A$ (γ-aminobutyric acid) receptor subtypes.
Modified from reference 35: Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300:2-8.

Sedation

Sedation is a major property of many benzodiazepine site ligands and has now been shown to be mediated via $GABA_A$ receptors. Among α_1-, α_2-, and α_3-point-mutated mice only the α_1(H101R) mutants were resistant to the depression of motor activity by diazepam and zolpidem.[45,46,48] This effect was specific for ligands of the benzo-diazepine site since pentobarbital or a neurosteroid remained as effective in α_1(H101R) mice as in wild-type mice in inducing sedation. An α_1(H101R) mouse line was also generated by McKernan et al[49] confirming that sedation is linked to α_1-$GABA_A$ receptors.

Amnesia

Anterograde amnesia is a classical side effect of benzodiazepine drugs. The memory-impairing effect of diazepam, analyzed in a step-through passive avoidance paradigm, was strongly reduced in the α_1(H101R) mice compared with wild-type mice, as shown by the increased latency for reentering the dark compartment 24 hours after training.[45] This effect was not due to a potential nonspecific impairment, since the ability of a muscarinic antagonist to induce amnesia was retained in the α_1(H101R) mice. These results demonstrate that diazepam-induced anterograde amnesia is mediated by α_1-$GABA_A$ receptors.

Protection against seizures

The anticonvulsant activity of diazepam, assessed by its protection against pentyleneterazole-induced tonic convulsions, was reduced in α_1(H101R) mice compared with wild-type animals.[45] Sodium phenobarbital remained fully effective as anticonvulsant in α_1(H101R) mice.

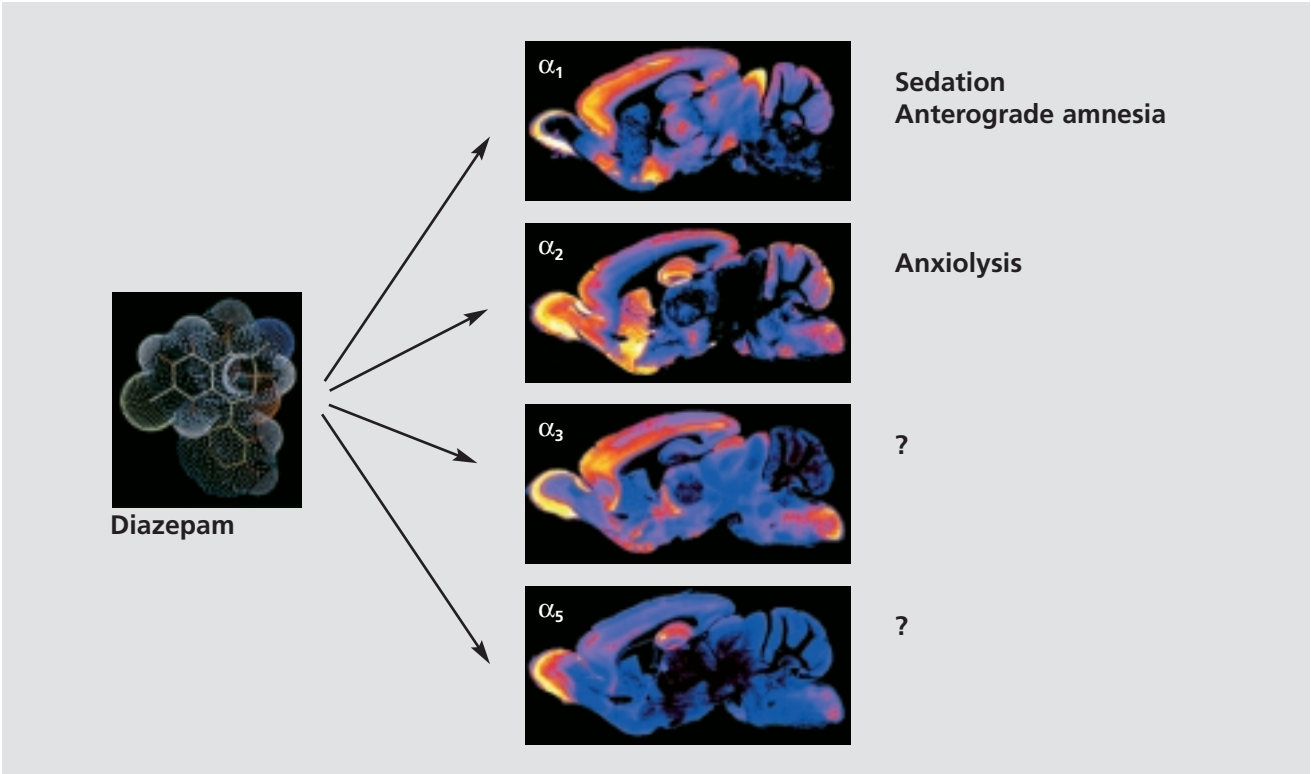


Figure 4. The four classes of diazepam-sensitive $GABA_A$ receptors are distinguished by the type of α-subunit (α_1, α_2, α_3, or α_5). Their largely distinct neuronal localizations are demonstrated immunohistochemically in mouse brain sections. The major known pharmacological actions mediated via the respective receptor subtypes are indicated. The α_5-$GABA_A$ receptors have recently been found to be involved in the formation of associative memory.[47]

Modified from reference 36: Rudolph U, Crestani F, Möhler H. $GABA_A$ receptor subtypes: dissecting their pharmacological functions. *Trends Pharmacol Sci*. 2001;22:188-194. Copyright © 2001, Elsevier Science Ltd.

These results show that the anticonvulsant activity of benzodiazepines is partially, but not fully mediated by α_1-GABA$_A$ receptors. The anticonvulsant action of zolpidem is exclusively mediated by α_1-GABA$_A$ receptors, since its anticonvulsant action is completely absent in α_1(H101R) mice.[48]

Anxiolysis

New strategies for the development of daytime anxiolytics that are devoid of drowsiness and sedation are of high priority. Experimentally, the anxiolytic-like activity of diazepam can be assessed by exposing wild-type animals to naturally aversive stimuli. For instance, in an elevated plus-maze test, the time spent on an open arm is enhanced after diazepam treatment, as is the time spent in the lit area of a light/dark choice test. In contrast, mice with a benzodiazepine-insensitive α_2-GABA$_A$ receptor (α_2(H101R)) were resistant to the effect of diazepam in these test paradigms.[46] Thus, the anxiolytic-like action of diazepam is attributed to the modulation of α_2-GABA$_A$ receptors. They are highly specific targets for the development of future selective anxiolytic drugs. The α_2-GABA$_A$ receptors, which comprise only about 15% of all diazepam-sensitive GABA$_A$ receptors, are mainly expressed in the amygdala and in principal cells of the cerebral cortex and the hippocampus with particularly high densities on their axon initial segments.[50,51] Thus, the inhibition of the output of these principal neurons appears to be a major mechanism of anxiolysis.

It had previously been assumed that the anxiolytic action of diazepam is based on the dampening of the reticular activating system. It is mainly represented by noradrenergic and serotonergic neurons of the brain stem, which express exclusively α_3-GABA$_A$ receptors. The analysis of the α_3-point-mutated mice (α_3(H126R)) indicated that the anxiolytic effect of benzodiazepine drugs, measured as described above, is not mediated by α_3-GABA$_A$ receptors.[46] The reticular activating system therefore does not appear to be a major contributor to anxiolysis. The role of α_3-GABA$_A$ receptors remains to be identified.

Myorelaxation

The muscle relaxant effect of diazepam is largely mediated by α_2-GABA$_A$ receptors, as shown by the failure of diazepam to induce changes in muscle tone in the α_2-point-mutated mouse line.[52] In addition to the areas described above, α_2-GABA$_A$ receptors are expressed in the spinal cord, notably in the superficial layer of the dorsal horn and in motor neurons,[53] the latter being most likely implicated in muscle relaxation. It is important to note that the muscle relaxant effect requires considerably higher doses of diazepam than its anxiolytic-like activity, which is mediated by α_2-GABA$_A$ receptors located in the limbic system (see above). Thus, a higher receptor occupancy seems to be required for muscle relaxation compared with the anxiolytic-like action of diazepam. It was only at very high doses of diazepam that α_3-GABA$_A$ receptors were also implicated in mediating myorelaxation.[52] ❑

I thank my colleagues D. Benke, F Crestani, J. M. Fritschy, B. Linscher, and U. Rudolph for their great contributions.

REFERENCES

1. Martina M, Schultz JH, Ehmke H, Monyer H, Jonas P. Functional and molecular differences between voltage-gated K+ channels of fast-spiking interneurons and pyramidal neurons of rat hippocampus. *J Neurosci*. 1998;18:8111-8125.
2. Geiger JR, Lubke J, Roth A, Frotscher M, Jonas P. Submillisecond AMPA receptor-mediated signalling at a principal neuron-interneuron synapse. *Neuron*. 1997;18:1009-1023.
3. Scanziani M. GABA spillover activates postsynaptic GABA(B) receptors to control rhythmic hippocampal activity. *Neuron*. 2000;25:673-681.
4. Alger BE, Le Beau FEN. Physiology of the GABA and glycine systems In: Möhler H, ed. *Pharmacology of GABA and Glycine Neurotransmission*. New York, NY: Springer; 2001:3-76.
5. Whittington MA, Traub RD, Faulkner HJ, et al. Synchronized oscillations in interneuron network driven by metabotropic glutamate receptor activation. *Nature*. 1995;373:612-615.
6. Whittington MA, Traub RD, Faulkner HJ, et al. Recurrent excitatory postsynaptic potentials induced by synchronized fast cortical oscillations. *Proc Natl Acad Sci U S A*. 1997;94:12198-12203.
7. Buhl EH, Tamas G, Fisahn A. Cholinergic activiation and tonic excitation induce persistent gamma oscillations in mouse somatosensory cortex in vitro. *J Physiol (Lond)*. 1998;513:117-126.
8. Fisahn A, Pike FG, Buhl EH, et al. Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. *Nature*. 1998;394:186-189.
9. Penttonen M. Gamma frequency oscillation in the hippocampus of the rat: intracellular analysis in vivo. *Eur J Neurosci*. 1998;10:718-728.
10. Zhang Y, Perez Velazquez JL, Tian GF, et al. Slow oscillations (≤1 Hz) mediated by GABAergic interneuronal networks in rat hippocampus. *J Neurosci*. 1998;18:9256-9268.
11. McCormick DA, Bal T. Sleep and arousal: thalamocortical mechanisms. *Ann Rev Neurosci*. 1997;20:185-215.
12. Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. *Ann Rev Neurosci*. 1995;18:555-586.
13. Laurent G. Dynamical representation of odors by oscillating and evolving neural assemblies. *Trends Neurosci*. 1996;19:489-496.
14. Traub RD, Whittington MA, Stanford IM, et al. A mechanism for generation of long-range synchronous fast oscillations in the cortex. *Nature*. 1996;383:621-624.

Aspectos fisiopatológicos de la diversidad en la inhibición neuronal: una nueva farmacología benzodiazepínica

Las interneuronas inhibitorias en el cerebro permiten equilibrar las señales excitatorias. En base a los estudios de neuroimágenes y de genética humana se ha identificado que un déficit de la inhibición gabaérgica (ácido gama amino butírico) contribuye a la fisiopatología de los trastornos de ansiedad, la epilepsia y la esquizofrenia. Los receptores $GABA_A$ juegan un rol principal como blancos para la acción terapéutica de las drogas benzodiazepínicas. Sólo recientemente ha sido identificada la importancia terapéutica de un sinnúmero de subtipos, estructuralmente diversos, del receptor $GABA_A$. Se encontró que los receptores $GABA_A\alpha_1$ mediaban la sedación, la amnesia anterógrada y parte de la protección contra las convulsiones de estas drogas, mientras que los receptores $GABA_A\alpha_2$, pero no los receptores $GABA_A\alpha_3$, mediaban la ansiolisis. Actualmente ha llegado a ser posible contar con drogas dirigidas racionalmente contra subtipos específicos del receptor. Sólo redes neuronales restringidas serán moduladas por la aparición de drogas subtipo selectivas. Por ejemplo, ansiolíticos exentos de somnolencia y sedación prometen intervenciones más sofisticadas para los trastornos de ansiedad. En el horizonte se cuenta con una nueva farmacología del sitio benzodiazepínico.

Aspects physiopathologiques de la diversité dans l'inhibition neuronale : une nouvelle pharmacologie des benzodiazépines

Les interneurones inhibiteurs du cerveau assurent l'équilibre des signaux de l'excitation. L'imagerie cérébrale et la génétique humaine ont montré qu'un déficit dans l'inhibition GABAergique (GABA, acide γ-aminobutyrique) contribuait à la physiopathologie de l'anxiété, de l'épilepsie et de la schizophrénie. Sur le plan thérapeutique, les récepteurs $GABA_A$ jouent un rôle majeur en tant que cible des benzodiazépines. Ce n'est que récemment que l'importance thérapeutique de la multitude des sous-types de récepteurs $GABA_A$ a été reconnue. Les récepteurs α_1-$GABA_A$ sont des médiateurs dans la sédation, l'amnésie antérograde et participent à l'activité protectrice des benzodiazépines dans la crise d'épilepsie, alors que les récepteurs α_2-$GABA_A$ - mais pas les récepteurs α_3-$GABA_A$ - sont des médiateurs de l'anxiolyse. Il est désormais possible d'utiliser de façon ciblée les molécules spécifiques des divers sous-types de récepteurs. Les prochains médicaments sélectifs pour les sous-types de récepteurs ne moduleront que des réseaux neuronaux limités. C'est ainsi que des anxiolytiques dénués d'effets sédatifs ou de somnolence permettront une efficacité plus marquée dans les troubles anxieux. Une nouvelle pharmacologie des sites benzodiazépiniques pointe à l'horizon.

15. Weiller E, Bisserbe JC, Maier W, Lecrubier Y. Prevalence and recognition of anxiety syndromes in five European primary care settings. A report from the WHO study on Psychological Problems in General Health Care. *Br J Psychiatry Suppl*. 1998;173:18-23.

16. Kalueff A, Nutt DJ. Role of GABA in memory and anxiety. *Depress Anxiety*. 1997;4:100-110.

17. Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain $GABA_A$-benzodiazepine receptor binding in panic disorders: preliminary results from a quantitative PET study. *Arch Gen Psychiatry*. 1998;55:715-720.

18. Malizia AL. What do brain imaging studies tell us about anxiety disorders? *J Psychopharmacol*. 1999;13:372-378.

19. Tiihonen J, Kuikka J, Rasenen P, et al. Cerebral benzodiazepine receptor binding and distribution in generalized anxiety disorders: a fractal analysis. *Mol Psychiatry*. 1997;6:463-471.

20. Goddard AW, Mason GF, Almai A, et al. Reductions in occipital cortex GABA levels in panic disorder detected ^{1}H MRS. *Arch Gen Psychiatry*. 2001;58:556-561.

21. Nutt DJ, Malizia AL. New insights into the role of the $GABA_A$ receptor in psychiatric disorders. *Br J Psychiatry*. 2001;179:390-396.

22. Crestani F, Lorez M, Baer K, et al. Decreased $GABA_A$ receptor clustering results in enhanced anxiety and a bias for threat cues. *Nat Neurosci*. 1999;2:833-839.

23. Eysenck MW. The nature of anxiety In: Gale A, Eysenck MW, eds. *Handbook of Individual Differences: Biological Perspectives*. New York, NY: Wiley; 1992:157-178.

24. Möhler H. Functions of GABA receptors: pharmacology and pathophysiology In: Möhler H, ed. *Pharmacology of GABA and Glycine Neurotransmission*. New York, NY: Springer Publishers; 2001:101-116.

25. Baulac S, Huberfeld G, Gourfinkel-An I, et al. First genetic evidence of $GABA_A$ receptor dysfunction in epilepsy: a mutation in the γ_2-subunit gene. *Nat Genet*. 2001;28:46-48.

26. Wallace RH, Marini C, Petrou S, et al. Mutant $GABA_A$ receptor γ_2-subunit in childhood absence epilepsy and febrile seizures. *Nat Genet*. 2001;28:49-52.

27. Minassian BA, DeLorey TM, Olsen RW, et al. Angelman syndrome: correlations between epilepsy phenotypes and enotypes. *Ann Neurol*. 1998;43:485-493.

28. Snead OC 3rd, Depaulis A, Vergnes M, Marescaux C. Absence epilepsy: advances in experimental animal models. *Adv Neurol.* 1999;79:253-278.

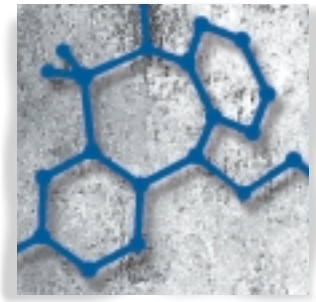
29. Meldrum BS, Whiting P. Anticonvulsants acting on the GABA system. In: Möhler H, ed. *Pharmacology of GABA and Glycine Neurotransmission*. New York, NY: Springer; 2001:173-194.

30. Woo TU, Whitehead RE, Melchitzky DS, et al. A subclass of prefrontal GABA axon terminals are selectively altered in schizophrenia. *Proc Natl Acad Sci U S A*. 1998;95:5341-5346.

31. Huntsman MM, Tran BV, Potkin SG, et al. Altered ratios of alternatively spliced γ_2 subunit of mRNAs of $GABA_A$ receptors in prefrontal cortex of schizophrenics. *Proc Natl Acad Sci U S A*. 1998;95:15066-15071.
32. Sarter M, Bruno JP, Berntson GG. Psychotogenic properties of benzodiazepine receptor inverse agonists. *Psychopharmacology*. 2001;156:1-13.
33. Mrzljak L, Bergson C, Pappy M, et al. Localization of D_4 receptors in GABAergic neurons in primate brain. *Nature*. 1996; 381:245-248.
34. Carlsson A, Waters N, Holm-Waters S, et al. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Ann Rev Pharmacol Toxicol*. 2001;41:237-260.
35. Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300:2-8.
36. Rudolph U, Crestani F, Möhler H. $GABA_A$ receptor subtypes: dissecting their pharmacological functions. *Trends Pharmacol Sci*. 2001;22:188-194.
37. Möhler H, Crestani F, Rudolph U. $GABA_A$-receptor subtypes: a new pharmacology. *Curr Opin Pharmacol*. 2001;1:22-25.
38. Brickley SG, Cull-Candy SG, Farrant M. Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of $GABA_A$ receptors. *J Physiol (Lond)*. 1996;497:753-759.
39. Mody I, Nusser Z. Differential activation of synaptic and extrasynaptic $GABA_A$ receptors. *Eur J Neurosci*. 2000;11(suppl 12):398.
40. Devor A, Fritschy JM, Yarom Y. Synaptic and extrasynaptic $GABA_A$ receptors in the inferior olivary nucleus differ in their spatial distribution, desensitization kinetics and subunit composition. *J Neurophysiol*. 2001;85:1686-1696.
41. Moss SJ, Smart TG. Constructing inhibitory synapses. *Nat Rev Neurosci*. 2001;2:240-250.
42. Fritschy JM, Möhler H. $GABA_A$ receptor heterogeneity in the adult rat brain: differential regional and cellular distribution of seven major subunits. *J Comp Neurol*. 1995;359:154-194.
43. Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. $GABA_A$ receptors immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience*. 2000;101:815-850.
44. Barnard EA, Skolnick P, Olsen RW, et al. Subtypes of γ-aminobutyric $acid_A$ receptors: classification on the bases of subunit structure and receptor function. *Pharmacol Rev*. 1998;50:291-313.
45. Rudolph U, Crestani F, Benke D, et al. Benzodiazepine actions mediated by specific γ-aminobutyric $acid_A$ receptor subtypes. *Nature*. 1999;401:796-800.
46. Löw K, Crestani F, Keist R, et al. Molecular and neuronal substrate for the selective attenuation of anxiety. *Science*. 2000;290:131-134.
47. Crestani F, Keist R, Fritschy JM, et al. Trace fear conditioning involves hippocampal α_5 $GABA_A$ receptors. *Proct Natl Acad Sci U S A*. 2002;99:8980-8985.
48. Crestani F, Martin JR, Möhler H, et al. Mechanism of action of the hypnotic zolpidem in vivo. *Br J Pharmacol*. 2000;131:1251-1256.
49. McKernan RM, Rosahl TW, Reynolds DS, et al. Sedative but not anxiolytic properties of benzodiazepines are mediated by the $GABA_A$ receptor α_1 subtype. *Nat Neurosci*. 2000;3:587-592.
50. Nusser Z, Sieghart W, Benke D, et al. Differential synaptic localization of two major γ-aminobutyric acid type: a receptor α subunits on hippocampal pyramidal cells. *Proc Natl Acad Sci U S A*. 1996;93:11939-11944.
51. Fritschy JM, Johnson DK, Mohler H, et al. Independent assembly and subcellular targeting of $GABA_A$ receptor subtypes demonstrated in mouse hippocampal and olfactory neurons in vivo. *Neurosci Lett*. 1998;249:99-102.
52. Crestani F, Löw K, Keist R, et al. Molecular targets for the myorelaxant action of diazepam. *Mol Pharmacol*. 2001;59:442-445.
53. Bohlhalter S, Weinmann O, Möhler H, et al. Laminar compartmentalization of $GABA_A$ receptor subtypes in the spinal cord: an immunohistochemical study. *J Neurosci*. 1996;16:283-297.

Psychopharmacology of anxiety disorders

Giovanni B. Cassano, MD; Nicolò Baldini Rossi, MD; Stefano Pini, MD



Exposure of the general population to a 1:4 lifetime risk of disabling anxiety has inspired generations of fundamental and clinical psychopharmacologists, from the era of the earliest benzodiazepines (BZ) to that of the selective serotonin reuptake inhibitors (SSRIs) and related compounds, eg, the serotonin and norepinephrine reuptake inhibitors (SNRIs). This comprehensive practical review summarizes current therapeutic research across the spectrum of individual disorders: generalized anxiety disorder (GAD), panic disorder (PD) and agoraphobia (social anxiety disorder), compulsive disorder (OCD), phobic disorder (including social phobia), and posttraumatic stress disorder (PTSD). Specific diagnosis is a precondition to successful therapy: despite substantial overlap, each disorder responds preferentially to specific pharmacotherapy. Comorbidity with depression is common; hence the success of the SSRIs, which were originally designed to treat depression. Assessment (multidomain measures versus individual end points) remains problematic, as—frequently—do efficacy and tolerability. The ideal anxiolytic remains the Holy Grail of worldwide psychopharmacologic research.

Dialogues Clin Neurosci. 2002;4:271-285.

Keywords: *generalized anxiety disorder; panic disorder; social anxiety disorder; posttraumatic stress disorder; obsessive compulsive disorder; benzodiazepine; antidepressant*

Anxiety disorders are the most common and among the most disabling of mental disorders in adults and adolescents.[1] Although many are highly circumscribed fears of mild-to-moderate severity, it has been estimated by the Epidemiological Catchment Area (ECA) study[2] that approximately one quarter of people will experience severe symptoms, disability, and handicap as a consequence of anxiety disorders at some time during their lifetime. These disorders are associated with significant morbidity[3] and increased mortality, probably as a consequence of increased suicide rates among sufferers. The direct and indirect costs to the health service and economy are considerable. Although persons who suffer from anxiety disorders are high consumers of all types of health services, only a minority receive specific help.[4]

The spectrum of anxiety disorders includes generalized anxiety disorder (GAD), panic disorder (PD) and agoraphobia, obsessive-compulsive disorder (OCD), phobic disorder (including social phobia), and posttraumatic stress disorder (PTSD). With the discovery of new psychotropic medications, specific diagnosis within this spectrum is essential because each of these disorders responds to specific pharmacotherapy. The approach to anxiety should also recognize that anxiety and depression are often comorbid conditions.

Selective serotonin reuptake inhibitors (SSRIs), which were designed to treat depression, are also effective for many anxiety disorders. They have revolutionized the treatment of anxiety, replacing chronic use of benzodiazepines (BZs). SSRIs are effective for OCD, PDs,

Author affiliations: Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnology, University of Pisa, Pisa, Italy

Corresponding author: Stefano Pini, MD, Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnology, University of Pisa, Pisa, Italy (e-mail: s.pini@psico.med.unipi.it)

Pharmacological aspects

Selected abbreviations and acronyms

BZ	*benzodiazepine*
GABA	*γ-aminobutyric acid*
GAD	*generalized anxiety disorder*
MAOI	*monoamine oxidase inhibitors*
OCD	*obsessive-compulsive disorder*
PD	*panic disorder*
PTSD	*posttraumatic stress disorder*
RIMA	*reversible inhibitor of monoamine oxidase A*
SNRI	*serotonin and norepinephrine reuptake inhibitor*
SRI	*serotonin reuptake inhibitor*
SSRI	*selective serotonin reuptake inhibitor*
TCA	*tricyclic antidepressant*

phobias, PTSD, and GAD *(see Table I)*. Other antidepressants, including tianeptine, have proven effective in adjustment disorders in which both anxiety and depression are involved. Doses of SSRIs for anxiety disorders could be higher than those used for depression, but must be started at lower doses to minimize the short-term agitation sometimes experienced with these medications. The patient should be counseled that side effects often diminish with time and also that empirical switching to another SSRI may be necessary.

Although tricyclic antidepressants (TCAs) have been used with success in anxiety disorders *(Table I)*, drowsiness, anticholinergic side effects, and toxicity have made these medications less popular. Also, monoamine oxidase inhibitors (MAOIs) are effective for anxiety, but their dietary restrictions and side-effect profile have limited their use.

BZs are the oldest class of medications used to treat anxiety. Although they have the advantage of rapid onset of action, they carry the risk of dependence, sedation, and tolerance. Withdrawal syndromes resulting in rebound anxiety, even reactions as severe as delirium tremens, are possible. BZs should be avoided in patients with a past history of substance abuse, personality disorder, or dosage escalation. These medications are ideal for patients who experience infrequent bouts of anxiety or episodes of anxiety-related insomnia.

Buspirone is a nonbenzodiazepine indicated for GAD. In head-to-head trials, it works as well as BZs for GAD, but has a slower onset of action and lacks sedative properties. It is therefore less useful for the anxious patient who needs a sedative. It does not impair alertness and lacks abuse potential.

A number of well-controlled clinical trials support the empirical evidence of effective pharmacotherapy of anx-

Medication	Starting dose (mg)	Therapeutic range (mg/day)	Common side effects	Indications (underscore indicates FDA approval)
• *Tricyclic antidepressants*				
Clomipramine	25	25-250	Weight gain, sedation, dry mouth	OCD, PD/AG, PTSD, GAD
Imipramine	10-25	150-300	Sedation, dry mouth	PD/AG, GAD, PTSD
• *Selective serotonin reuptake inhibitors*				
Citalopram	10	10-60	Nausea, somnolence, dry mouth	PD/AG, OCD, PTSD, SAD, GAD
Fluoxetine	5-10	10-80	Nausea, anorexia, insomnia, somnolence	OCD, PD/AG, PTSD, SAD, GAD
Fluvoxamine	50	50-300	Nausea, insomnia, somnolence, headache	OCD, PD/AG, PTSD, SAD, GAD
Paroxetine	10	10-50	Nausea, somnolence, ejaculation failure	OCD, PD/AG, SAD, PTSD, GAD
Sertraline	25	50-200	Nausea, insomnia, ejaculation failure	OCD, PD/AG, PTSD, SAD, GAD
• *Novel antidepressants*				
Venlafaxine	37.5	37.5-300	Nausea, dry mouth, insomnia, dizziness	GAD, PD/AG
• *Other medications*				
Buspirone	5 (bid)	15-60	Dizziness, nausea	GAD
Propranolol	20	20-160	Depression, sedation	Performance anxiety
• *Benzodiazepines*				
Alprazolam	0.25 (tid)	0.25-4	Drowsiness, withdrawal	GAD, PD/AG, PTSD
Clonazepam	0.25 (bid)	0.25-4	Somnolence, fatigue, depression	PD/AG, GAD, PTSD
Lorazepam	0.5 (tid)	1-6	Sedation, dizziness	GAD, PD/AG, SAD

Table I. Common medications used in the treatment of anxiety. FDA, Food and Drug Administration; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PD/AG, panic disorder/agoraphobia; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

iety disorders. However, the ideal anxiolytic does not exist, and current research into some new compounds is very active and promising. Pharmacological treatment evidence for each anxiety disorder will be briefly reviewed.

Generalized anxiety disorder

Benzodiazepines

Several studies have documented that BZs are more effective than placebo in GAD.[5-9] There is also evidence that BZs may be more effective on specific GAD symptoms, particularly the somatic/autonomic symptoms in contrast to the psychic symptom cluster, which includes apprehensive worry and irritability.[10] For example, several studies have shown that irritability may worsen in conjunction with high-potency BZs,[11] and that low levels of depressive symptoms may predict a less favorable response to BZs.[9] Other data suggest that, although they respond less well to BZs, psychic symptoms may be more responsive to other drugs altogether, such as buspirone or imipramine.[9-10,12] Overall, BZs still remain a widely used treatment option for GAD, partly no doubt because of their rapid onset of action, with maximum effect achieved within 2 weeks, and their generally good tolerance[9,13]; however, there are few controlled data to support continued benefits of BZs in the long term in GAD. Information from some 6 to 8 months' maintenance therapy trials have found continued efficacy over time,[14-17] but since GAD is often a long-term and unremitting disorder,[18] it needs to be stated that pharmacotherapy, whether with BZs or other drugs, may need to continue for many years in a significant number of patients.

Results generally show that approximately 70% of patients will respond to adequate BZ treatment (up to 40 mg/day of diazepam or equivalent for at least 3-4 weeks), but less than two thirds will achieve remission of symptoms. In long-term use, tolerance to side effects does occur, but tolerance to the anxiolytic effect of the BZs does not appear.[19] With regard to dependence and withdrawal, compounds with a slower onset of action, for example, oxazepam, have little reinforcing potential, while those with a long half-life, for example, diazepam and chlordiazepoxide, have a lower propensity to produce withdrawal symptoms, even if stopped abruptly. Anyway, discontinuation of acute treatment should be slow because of the potential for rebound anxiety and/or clinical relapse, and an adequate pretreatment assessment should be an important step to evaluate whether a subject would be suitable for BZ therapy, including previous history of withdrawal, liability of abuse, or likelihood of poor compliance. For this reason, and because of the high prevalence of comorbid depression, attention has focused also on different medications and antidepressants as potential treatment for GAD *(Table II)*.

Azapirones

The first pharmacological treatment for GAD beyond BZs was the azapirone buspirone, a partial 5-hydroxytryptamine (serotonin, 5-HT)–1A (5-HT_{1A}) agonist, which decreases the function of postsynaptic 5-HT_2 receptors. It has been demonstrated to show efficacy in GAD[10,20-22] and has been associated with maintenance of efficacy over a period of several months.[15,16]

Buspirone is given in two or three divided doses up to 60 mg/day, and its effect is usually not apparent until 2 to 3 weeks into treatment, in contrast to the almost immediate effects of BZs. It is not sedating like the BZs; it is not associated with psychomotor impairment, tolerance, dependence, or withdrawal; and it does not interact with alcohol.

Predominant clinical features	First-line treatment	Partial or no response
• Somatic and autonomically driven symptoms • History of abuse absent • Sedation is needed	***BZ***	Add or switch to a medication from a different class from the starting medication: ***SSRI*** or ***TCA*** or ***buspirone*** or ***BZ***
• Psychic symptoms (apprehensive worry, tension, irritability) • Presence of history of abuse • Sedation is not needed or is contraindicated	***Buspirone***	
• Depressive symptoms are intermixed with anxiety • BZs or buspirone are contraindicated	***SSRI*** or ***TCA*** or ***trazodone***	Add ***buspirone*** or ***BZ***

Table II. Generalized anxiety disorder (GAD): therapeutic strategies. BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

The drug works well when there are conspicuous symptoms of worry, apprehensive tension, and irritability,[10] and where depressive symptoms are intermixed with anxiety,[23] while it is less effective than BZs on somatic and autonomically driven symptoms.[24,25] Patients who have had previous good responses to BZs do not appear to respond as well to buspirone,[22] probably due to the lack of sedative effect and inability to alleviate BZ withdrawal symptoms, but starting buspirone 2 to 3 weeks before tapering the BZs has produced better results.[26]
Other azapirone drugs have been assessed in GAD, like gepirone,[27,28] ipsapirone,[29] and more recently flesinoxan and tandospirone, but with more equivocal results.

Antidepressants

Although antidepressants are now well-established treatments of choice in several anxiety disorders (eg, PD, social phobia, OCD, and PTSD), their role in the treatment of GAD remains unclear. Little attention has been given to the fact that several studies have provided encouraging support for their efficacy. Perhaps the obscurity of these findings relates to the general uncertainty about the nature of GAD, its constantly changing criteria, and the apparent belief that it is a highly placebo-responsive disorder.[30] Early retrospective analyses of subjects with anxiety neurosis[21,31] have supported the possible efficacy of tricyclic drugs in GAD-like states. Further controlled trials by Kahn et al,[32] Hoehn-Saric et al,[12] and Rickels et al[9] have provided evidence for the benefit of imipramine and trazodone in GAD. Imipramine was more effective than diazepam on psychic anxiety symptoms, and it would also be expected to have significant antidepressant effects. Its reuptake-inhibiting effects on serotonin and norepinephrine confer a double advantage relative to some of the more selective compounds mentioned above.
Trazodone, a serotonin reuptake inhibitor (SRI) and 5-HT_2 receptor antagonist, has also been found to be effective and remains a little-used, but potentially effective drug for the disorder at doses of up to 400 mg/day, with doses of 200 to 300 mg/day often being sufficient. However, due to its side-effect profile, trazodone is unlikely to be a first choice, but can be a useful backup drug for more difficult to treat or nonresponsive patients. Its hypnotic properties are also useful where insomnia is a major problem.
Nefazodone is a combined SRI, 5-HT_2 antagonist, and weak adrenergic antagonist, which may also be beneficial in GAD. Nefazodone enjoys the advantage of greater patient acceptability and tolerability than trazodone. One open-label study in GAD has suggested benefit for this drug,[33] as is also the case for the SSRI paroxetine.[34]
The most recent development in the pharmacotherapy of GAD, largely out of consideration of the results of the studies with TCAs, has been the controlled comprehensive trials with venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI). In five placebo-controlled 8-week trials, venlafaxine has demonstrated efficacy significantly greater than placebo in the treatment of GAD patients without accompanying depression. Venlafaxine (75, 150, and 225 mg/day) produced greater effects than placebo after 1 week of the study, and these improvements were maintained throughout the remainder of trials.[35,36] These findings were replicated in a large 6-month trial evaluating long-term treatment of GAD. Although most of the improvement on venlafaxine occurred in the first 4 weeks, subjects continued to improve over the 6-month period.[37,38] Current trials have not established an optimal dosage for venlafaxine in the treatment of GAD, with positive results observed at dosages as low as 37.5 mg/day. However, data suggest that 75 to 150 mg/day is probably the most appropriate dosage range. Mild side effects including nausea, insomnia, dry mouth, and dizziness were principally seen at the initiation of treatment and cleared up over time.
Another double-blind, 8-week study compared venlafaxine (up to 150 mg/day), with buspirone (up to 30 mg/day), and placebo in outpatients with GAD. Both drugs were superior to placebo, but venlafaxine showed an earlier effect and advantage over buspirone in secondary outcome measures, notably the Hamilton Depression Scale anxiety subscore.[39]
The results of these studies indicate that antidepressants offer promise in GAD, even if they appear to be better in treating psychic anxiety symptoms, while BZs are probably superior in treating the somatic symptoms.[40]

Other drugs

Several other drugs have been assessed in GAD. The well-established anxiolytic effects of BZs are modified by several drawbacks, primarily of physical dependence, withdrawal symptoms, and sedation. The development of partial agonists at the γ-aminobutyric acid (GABA)/BZ receptor complex offers some potential advantages over the traditional BZs. These BZ-like compounds

should be effective anxiolytics, but less likely to produce sedation, tolerance, withdrawal, abuse liability, memory impairment, and ethanol potentiation. These newly developed compounds are either BZ derivatives or of a different chemical structure, that is, imidazopyridine and β-carbolines. The most comprehensively studied has been the β-carboline abecarnil. In an initial double-blind trial, Ballenger et al[41] demonstrated clinical efficacy at doses in the range of 3 to 9 mg/day, without withdrawal symptoms after short-term treatment. Further placebo-controlled studies[42,43] have shown modest treatment effects; however, at higher doses, there is some evidence of withdrawal symptoms.

Hydroxyzine, an antihistaminergic compound, has been reported to produce improvement in 60% to 90% of patients with GAD.[44] It can be very sedating when high doses are used (50 and 100 mg qid), but a more recent study[45] showed that it can be effective at low doses (50 mg/day) as well. After 5 weeks of treatment, 86% of the patients improved compared with 47% with placebo, and the drug was well tolerated.

β-Blockers have been used for the treatment of some anxiety disorders, but the evidence so far does not support their use in GAD.[46]

Finally, anecdotal experiences report potential value of kava and passionflower extract in the treatment of GAD.[47-49]

Panic disorder

Benzodiazepines

Alprazolam, the first licensed BZ for the treatment of panic, was studied in a large multinational placebo-controlled trial (Cross National Collaborative Panic Study) conducted in two 8-week phases: during the first it was compared with placebo, and then it was compared with both placebo and imipramine. Patients showed significant improvements in all major symptom areas, like number of panic attacks, avoidance behavior, and residual anxiety between attacks,[50,51] with improvements also maintained in longer-term studies.[52] Other high-potency BZs, such as clonazepam[53] and lorazepam,[19] showed similar efficacy. BZs are usually well tolerated and they have a rapid onset of action (1-2 weeks). Potential problems with long-term use of BZs in PD are tolerance, dependence, and withdrawal symptoms on discontinuation, but a 2.5-year naturalistic follow-up study found little evidence of tolerance to the antipanic effect of alprazolam, and efficacy was maintained without dose escalation.[54]

Although some studies have failed to observe a difference between alprazolam and imipramine in treatment of the common comorbid depressive symptoms,[55] several large meta-analyses have suggested a reduced efficacy for the BZs compared with TCAs[56] and antidepressants in general *(Table III)*.[57,58]

Antidepressants

Early in the 1960s, investigators documented that imipramine[59] and the MAOIs, particularly phenelzine,[60] were both effective treatments of PD.[61] Other TCAs also proved effective, especially clomipramine, and the improvement was not dependent on the treatment of concurrent affective symptoms. Following the demonstration of efficacy of the non-SSRI clomipramine, a number of large randomized trials have now demon-

Predominant clinical features	First-line treatment	Partial or no response
• Mild symptoms • No cardiovascular system pathology or seizure history • SSRI intolerability	***TCA*** (clomipramine, imipramine)	Add a ***mood stabilizer*** (valproate, lithium, gabapentin) or switch to an ***SSRI*** (eventually try ***venlafaxine*** or ***reboxetine***)
• Severe symptoms • High frequency of attacks • Invalidating symptoms • History of abuse absent	***High-potency BZ*** (alprazolam, clonazepam)	Add an ***SSRI***, a ***TCA***, or a ***mood stabilizer*** (valproate, lithium, gabapentin)
• SSRIs are not contraindicated	***SSRI***	Add a ***mood stabilizer*** (valproate, lithium, gabapentin) or switch to a ***TCA*** or a different ***SSRI*** (eventually try ***venlafaxine*** or ***reboxetine***)

Table III. Panic disorder (PD): therapeutic strategies. BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

strated the efficacy of SSRIs in PD, both in comparison with placebo and clomipramine. Well-controlled trials provided evidence[62] that fluvoxamine, paroxetine, citalopram, sertraline, and fluoxetine have similar efficacies, although comparison trials between different SSRIs are generally lacking. A recent effect-size analysis of controlled studies of treatment for PD also revealed no significant differences between SSRIs and older antidepressants in terms of efficacy or tolerability in short-term trials.[63] As has been observed in all the trials, effective treatments reduce all the symptoms of PD, the frequency and severity of panic attacks, agoraphobic avoidance, anxiety, and comorbid depression. Although there are different responses of each of these symptoms to these treatments (eg, agoraphobic avoidance is the most difficult to treat), successful treatments effectively reduce all these aspects of the PD syndrome, but appropriate outcome measures for PD still remain a problem.[64] Reduction of panic-attack frequency has been widely utilized, but has been unreliable as a single measure, and most investigators now use multidomain measures.[64]

The percentage of patients who become free of panic attacks is generally 50% to 80% in acute trials lasting 6 to 8 weeks with various medications.[65] In patients who are treated for longer periods, this percentage most often rises. It is generally true that the longer PD patients are treated, the more complete and comprehensive is their response. In the large Cross-National Collaborative Panic Study,[66] after 8 to 12 months of treatment, three fourths of patients were free of panic attacks. In a large 12-month comparison of paroxetine and clomipramine, the panic-free rates were 85% and 72%, respectively, rising from about 55% at 3 months.[67]

The anxiety that PD patients experience between panic attacks can be considerable. This anxiety is reduced by all effective therapies with little difference between treatments.[56,58] In a similar fashion, most effective treatments decrease the common comorbid depressive symptoms, again generally with little difference between treatments.[65]

Agoraphobia is probably the most treatment-resistant symptom in PD. Although effective pharmacotherapy does significantly reduce agoraphobia avoidance, in vivo exposure is often employed to reduce avoidance behaviors. There is no standard measure employed in the literature of improvement in agoraphobic avoidance, making comparisons across studies and treatments difficult. Nonetheless, in a review of 16 studies,[68] remission of agoraphobia occurred in ranges varying from 18% to 64%, and in a 12-month naturalistic study,[69] 69% of patients became free of avoidance.

Improvement in agoraphobic avoidance occurs with all the effective treatments, probably more or less equally, although this has not been rigorously studied. The BZs are as effective as antidepressants in reducing avoidance, although effects begin earlier with the BZs.[58] Improvement is seen as early as the first or second week with BZs and as early as the fourth week with the antidepressants,[70,71] although improvement in agoraphobia is often the last portion of the syndrome to respond, and patients continue to improve for at least 3 to 6 months. Recent trials suggest that a significant response to antidepressants may occur in the first 2 to 4 weeks, which is earlier than previously thought.[71,72] An important phenomenon in the early stages of treatment (both with TCAs and SSRIs) could be the paradoxical and transient increase in anxiety and number of panic attacks, the so-called "jittering syndrome." To initiate treatment at a very low dose, or to cover this first period with a high-potency BZ, such as clonazepam or alprazolam, could be useful approaches.

Dietary restrictions and side effects have limited the use of MAOIs, but the introduction of the reversible inhibitors of monoamine oxidase A (RIMAs), such as moclobemide, renewed the interest in this class of agents. The results, though, so far are conflicting, with an 8-week study showing efficacy for moclobemide in PD,[73] and another one failing to do so.[74]

A small case series suggested that venlafaxine may be effective in the treatment of PD,[75] and mirtazapine provided good evidence both in an open-label study with a single-blind placebo run-in period,[76] and in a 8-week double-blind comparison with fluoxetine.[77] Reboxetine, a selective norepinephrine reuptake inhibitor was effective and well tolerated in an 8-week, placebo-controlled, double-blind trial,[78] with a significant reduction in the mean number of panic attacks and phobic symptoms at doses of 6 to 8 mg/day.

Other drugs

Buspirone in PD failed to show any efficacy even at high doses (60 mg/day).[79] Pagoclone, a cyclopyrrolone that is believed to act as a partial agonist at the $GABA_A$/BZ receptor provided some preliminary evidence in a crossover trial with placebo.[80] β-Blockers provided con-

flicting results, with some positive small crossover trials, but a negative double-blind trial of propranolol with alprazolam and placebo.[81] Initial evidence suggested that gabapentin[82] and sodium valproate may be effective in PD, while carbamazepine is not.[83] Also Ca-channel blockers have shown mixed results.[84]

Social anxiety disorder

Benzodiazepines

There is a limited number of controlled studies testing BZs in the treatment of social anxiety disorder. Clonazepam was shown to be effective in one 10-week, double-blind trial versus placebo, with 78% of patients responding to an average dosage of 2.4 mg/day.[85] Almost 85% of patients had some response, with 50% having a marked response and 50% having a moderate one. There has been only one double-blind study of alprazolam, in which Gelernter et al[86] compared alprazolam (mean dose 4.2 mg/day) with phenelzine, cognitive behavioral group therapy, and placebo over a 12-week period. Only 38% of patients on alprazolam were considered responders at end point compared with 69% on phenelzine, 24% on cognitive behavioral group therapy, and 20% on placebo.

Versiani et al[87] conducted a 12-week, double-blind study to compare bromazepam (mean dose 21 mg/day) to placebo, with a response rate of 83% of patients on active drug versus 20% of patients on placebo.

Antidepressants

Only anecdotal evidence supports the efficacy of TCAs for the treatment of social anxiety disorder,[88] mainly due to early observations that patients with atypical depression with marked interpersonal sensitivity and sociophobic features show a better response with MAOIs than TCAs.[89]

There were three early controlled trials[86,90,91] in which phenelzine (up to 90 mg/day) was found to be quite effective, with 64% of patients obtaining clinically significant responses, which increased when treatment was extended to 4 months. These results were replicated by Heimberg et al[92] in 1998.

In a comparison between phenelzine and moclobemide, phenelzine appeared roughly equivalent, but appeared to work faster.[91] By week 16, 91% of the phenelzine patients versus 82% of moclobemide patients were nearly asymptomatic, although moclobemide was better tolerated. In the Gelernter et al[86] trial, phenelzine was also better than alprazolam in terms of efficacy.

As mentioned above, RIMAs have also been studied. Brofaromine (up to 150 mg/day) was promising and roughly comparable to moclobemide, with response rates of 80%,[93] 78%,[94] and 50%.[95] Moclobemide, after the promising results of Versiani et al,[91] produced a less robust result in the large multicenter controlled study that followed,[96] in which 600 mg/day was superior to placebo (47% of responders compared with 34% receiving placebo). Another large multicenter trial,[97] as well a single study,[98] failed to confirm the efficacy of this drug in social anxiety.

Certainly the greatest amount of carefully controlled data are from the recent paroxetine studies.[99-101] In multicenter, double-blind, placebo-controlled, 12-week trials in severely symptomatic patients with social phobia, 55% of patients had a marked or moderate response at a mean dosage of 36.6 mg/day. Scores on the Liebowitz Social Anxiety Scale fell about 40% on paroxetine (30.5 points). Differences were observed in the second week and throughout the remainder of the trial. These positive findings were confirmed by Baldwin et al[102] and Allgulander.[103]

Other controlled trials with SSRIs include fluvoxamine,[88,104] sertraline,[105,106] fluoxetine,[107] venlafaxine,[108] and nefazodone.[109] In these trials, the clinically significant response rates of patients were in the 42% to 77% range.

Finally, open trials of citalopram[110-112] and buproprion[113] have suggested that these drugs may be effective in the treatment of social anxiety disorder, but controlled studies are needed to confirm preliminary results.

Other drugs

Buspirone has been shown to be effective as a primary treatment in two thirds of patients in early trials,[114,115] as well as an augmenting agent with SSRIs.[116] One controlled trial failed to find significant differences between buspirone and placebo.[117] Also the β-blocker atenolol, despite early promise, proved ineffective when tested in patient populations with generalized symptoms of social phobia.[90,118] Pindolol was no more effective than placebo in augmenting the effects of paroxetine treatment for generalized social phobia.[119]

High doses of gabapentin (3600 mg/day) provided encouraging preliminary results in a 14-week, placebo-controlled study.[120] Pregabalin, a follow-up compound of the GABA agonist gabapentin, is being developed for the potential treatment of several central nervous system disorders and anxiety, including social anxiety disorder.[121]

Posttraumatic stress disorder

Benzodiazepines

PTSD is a complex syndrome occurring after one or more traumatic events and involves multiple anxiety symptoms, including flashbacks, emotional numbing, avoidance of the reminders of the event, and so forth. This disorder was first recognized after military combat, but is now seen frequently after rape, assault, and accidents. Although there is no established pharmacotherapy for PTSD, there are multiple medications that seem to be effective in reducing these symptoms, particularly flashbacks, phobic avoidance, depression, anxiety, startle reaction, impulsivity, and hypervigilance *(Table IV)*. BZs seem to be helpful in suppressing hyperarousal symptoms. The first placebo-controlled trial was conducted by Braun et al[122] using alprazolam up to 6 mg/day. Although the core symptoms of the syndrome (intrusion and avoidant/numbing symptoms) did not improve significantly compared with placebo, they reported a positive effect in subjective well-being and a reduction in anxiety, irritability, and insomnia. Open trials with alprazolam and clonazepam came to similar results,[123] but withdrawal symptoms were particularly severe, especially considering the substantial comorbidity of PTSD with alcohol and drug abuse.
O'Brien and Nutt[124] hypothesized that early BZ treatment of trauma survivors may protect toward future development of PTSD, but the data are still controversial, especially concerning how soon after the event treatment has to be started to offer this protection.[125]

Antidepressants

TCAs have been shown to be helpful in three controlled trials. Imipramine (up to 300 mg/day) decreased intrusive thoughts, nightmares, and flashbacks with no effect on numbing or avoidance in an 8-week study.[126,127] Amitriptyline (up to 300 mg/day) has also been shown to reduce avoidance and anxiety in an 8-week trial, but it had no effect in the re-experiencing of intrusive thoughts and images.[128] Desipramine failed to show any advantage over placebo in a 4-week study,[129] but at relatively low doses compared with the two previous trials. Moreover, as highlighted by Friedman,[123] TCAs have been tested mainly on samples of veterans with severe chronic PTSD, while SSRIs and MAOIs have been tested in nonveteran samples. An important finding arising from these studies is the lack of placebo response in PTSD compared with other anxiety disorders.
MAOIs have also been shown to be effective (phenelzine up to 75 mg/day) in reducing intrusive thoughts and flashbacks after 8 weeks of treatment,[126] but other trials have failed to observe positive effects.[130] MAOIs appear to produce moderate to good clinical improvement, primarily affecting PTSD intrusive recollections, flashbacks, and nightmares, while hyperarousal, numbing, and avoidance behavior are scarcely affected. In addition, the usual dietary and medication restrictions of the MAOIs are more problematic in this patient group, given the high incidence of substance abuse.[123] Early trials with combat veterans suggest that the reversible MAOI moclobemide is promising.[131]

Predominant clinical features	First-line treatment	Partial or no response
• Intusive thoughts and flashbacks, hyperarousal, impulsivity	***SSRI*** (fluoxetine, paroxetine, sertraline) or ***mood stabilizer*** (carbamazepine, lithium, valproate)	***SSRI*** and/or ***mood stabilizer*** (also topiramate and gabapentin) ***combination***
• Anxiety without severe depression, irritability, insomnia	***Alprazolam***, ***clonazepam***, or ***buspirone***	
• Depressive symptoms	***SSRI*** (fluoxetine, paroxetine, sertraline), or ***TCA*** (imipramine, amitriptyline), or phenelzine	Add ***nefazodone*** or ***trazodone*** for concurrent sleep disorders
• Psychotic symptoms, aggressivity, or agitation	***Olanzapine***	

Table IV. Posttraumatic stress disorder (PTSD): therapeutic strategies. SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

SSRIs have been observed to be helpful in open studies, especially with fluoxetine up to 80 mg/day.[132,133] This has been confirmed in a placebo-controlled trial of veteran and civilian trauma victims.[134] Approximately two thirds of patients experienced decreases in the core symptoms of PTSD including hyperarousal, numbing, avoidance, and intrusive images. Penava et al[135] conducted an effect-size analysis of controlled studies where fluoxetine showed the biggest effect compared with the other antidepressant and BZs studied so far.
Sertraline has also been reported effective[136] in long-term treatment[137,138] and paroxetine (20-40 mg/day) was superior than placebo in two recent 12-week, double-blind studies.[139,140]
Nefazodone (350-450 mg/day) has been shown to significantly improve most symptoms, including intrusive thoughts, avoidant behaviors, emotional numbing, nightmares, sleep, depression, and anger,[141,142] and there is only anecdotal evidence for improvement with trazodone.[123]

Other drugs

The anticonvulsant carbamazepine has been shown to decrease flashbacks, hyperarousal, and impulsivity.[143,144] Lithium and valproic acid may be helpful as well,[145-147] particularly in patients with poor impulse control.[148] Open-label topiramate[149] and gabapentin[150] appeared effective as add-on therapy for chronic PTSD.
Buspirone (15-35 mg/day) was reported to be effective in reducing anxiety, insomnia, flashbacks, and depressed mood in three PTSD war veterans after 2 weeks of treatment.[151]
Some case reports with atypical neuroleptics and an open-label study with olanzapine have been positive for the treatment of the core symptoms and the psychotic symptoms that PTSD patients may exhibit.[123,152]
Open-label propranolol (120-160 mg/day) improved hyperarousal, sleep, nightmares, explosiveness, and psychosocial functioning in 11 out of 12 Vietnam veterans,[153] and acute, posttrauma propranolol may have a preventive effect on subsequent PTSD.[154]
The α_1-adrenergic antagonist prazosin[155] and α_2-adrenergic agonists clonidine and guanfacine also provided some preliminary promising results.[123,153]

Obsessive-compulsive disorder

Benzodiazepines

BZs are not a first-choice treatment for OCD *(Table V)*, and few data exist to date. Clonazepam, a BZ that also affects serotonergic transmission, was compared with clomipramine and clonidine in a crossover, double-blind study with each treatment lasting for 6 weeks.[156] The first two drugs were equally effective, while clonidine was largely ineffective. Clonazepam provided an early improvement (2-3 weeks), unrelated to changes in anxiety, and there was a significant cross-response between clomipramine and clonazepam, with patients who failed on clomipramine showing a clinically significant response to clonazepam.

Predominant clinical features	First-line treatment	Partial or no response
• Depressive symptoms, recurrent course with bipolar spectrum comorbidity	***SSRI*** Eventually ***switch to a different SSRI or SRI*** (clomipramine or intravenous clomipramine) (Potentiation ***with buspirone, clonazepam, tryptophan, pindolol***)	Add ***mood stabilizer*** (lithium, gabapentin)
• Highly anxious obsessional subjects		Add ***BZ*** (clonazepam)
• Prevalent symmetry and atypical obsession or high level of anxiety to treatment		Add ***MAOI*** or ***SNRI*** and eventually ***neuroleptic***
• Severe hoarding symptoms		Add different ***typical/atypical neuroleptic*** (pimozide, haloperidol, risperidone, olanzapine)
• Tics, psychotic symptoms		Add different ***typical/atypical neuroleptic*** (pimozide, haloperidol, risperidone, olanzapine)

Table V. Obsessive-compulsive disorder (OCD): therapeutic strategies. BZ, benzodiazepine; MAOI, monoamine oxidase inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

Pharmacological aspects

Antidepressants

Pharmacological investigations have demonstrated that OCD responds selectively to drugs that act as potent inhibitors of the synaptic reuptake of serotonin. The first medication demonstrated to be effective in OCD was clomipramine (150-250 mg/day) with 40% of patients (versus 4% for placebo) having a clinically significant decrease in symptoms independently of its antidepressant effect.[157-159] Subsequently, all of the SSRIs have been shown to be effective, including fluvoxamine (100-300 mg/day), fluoxetine (20-80 mg/day), paroxetine (40-60 mg/day), sertraline (50-200 mg/day), and citalopram (20-60 mg/day).[159] Most recent controlled trials find that about 50% of patients experience a 25% to 35% drop in scale scores of OCD, primarily utilizing the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). This magnitude of change typically results in significant improvement in function; however, interfering symptoms usually persist.
Relative efficacy between the SRIs has been difficult to determine. Two meta-analysis suggested greater efficacy for chlorimipramine[160,161]; however, these trials were performed over a 7- to 10-year time period, during which placebo rates rose significantly, making any conclusion suspect. In fact, in several head-to-head trials, clomipramine was found to have equal efficacy to fluoxetine,[162] paroxetine,[163] and sertraline,[164] with SSRIs being better tolerated than clomipramine. A more recent meta-analysis generally failed to find any significant difference between the SRIs, although it again suggested some advantage for clomipramine. However, this meta-analysis involved many of the trials mentioned above and has the same problem in interpretation.[165] There was no observed difference in a trial comparing fluvoxamine, paroxetine, and citalopram.[166]
Due to their similar effects, it is difficult to choose between SSRIs, and the selection of a drug largely depends upon personal preference, even if the possibility of a drug interaction or the various pharmacokinetic profiles could influence the choice. Dosages of these medications have often been described as being significantly higher than antidepressant dosages (eg, 60-80 mg/day fluoxetine); however, in large carefully controlled trials, there has been no observed significant difference between response to higher and lower dosages for the SSRIs (eg, 50 and 200 mg/day sertraline).[167] This clinical impression may well relate to the slow onset of effectiveness with many patients taking 10 to 12 weeks to improve (longer than 4-8 weeks for depression), during which physicians continue to raise the patients' doses, mistakenly thinking it was the increased dose, not time, that was responsible for improvement. For this reason, it is helpful to warn patients about this from the outset, and slowly titrate doses upwards to avoid side effects.
Many patients will not respond or will partially respond to the first SSRI, but will respond to another antiobsessional agent. Therefore, sequential trials are frequently required, which easily can take up to a year to accomplish.
Limited available evidence suggests that when effective pharmacotherapy is discontinued, most patients (90%) do relapse.[168] Therefore, current practice is to continue effective pharmacotherapy for at least 1 to 2 years or indefinitely. In a large extension study by Greist et al,[167] 118 patients who had responded to 12 weeks' treatment with either sertraline or placebo continued their treatment, in a double-blind way, for 40 weeks. Therapy gains with sertraline were maintained with continued medication as long as they remained on active medication, without tolerance developing. The 59 patients who completed this study were followed up for a second year on open-label sertraline, whereupon they showed additional clinical improvements.[169] Another trial with paroxetine demonstrated continued efficacy for 12 months in the majority of patients.[170]
The effectiveness of potent SRIs is now well established in the treatment of OCD, but despite these advances, nearly 40% to 60% of patients experience minimal to no improvement in symptoms with these treatments. Furthermore, in patients who do respond to SRIs, the degree of improvement is often incomplete, with few patients experiencing full symptom remission.[171] For these reasons, attempts to augment or improve the average response with pharmacological strategies targeting serotonergic or other neurotransmitter systems are routine. There is no agent that is routinely effective as an augmenting agent, although there is some support for clonazepam, clonidine, trazodone, nefazodone, tryptophan, and pindolol.[172] There is clear evidence of benefit for traditional neuroleptics[173] and more recently the atypical neuroleptics (eg, risperidone, olanzapine, and quetiapine), principally in the patients with OCD who have comorbid tic disorders.[174-177]
Intravenous clomipramine has also been shown to be more effective than oral administration.[178,179]
Two controlled studies were performed to test the

MAOI phenelzine efficacy in OCD. The first one[180] found phenelzine (up to 75 mg/day) and clomipramine (up to 225 mg/day) both effective with no significant difference between the two drugs, while another one comparing phenelzine (60 mg/day) with fluoxetine (80 mg/day) and placebo found that phenelzine was no better than placebo.[181]

Other drugs

Buspirone produced an effect similar to clomipramine in a small double-blind study with 18 patients,[182] but the results from controlled trials of buspirone augmentation to SRIs were less encouraging.[183,184]

Inositol (18 mg/day) was superior to placebo and well tolerated in a short-term, double-blind, controlled trial with crossover design performed in OCD.[185]

Lithium has been suggested to further reduce obsessive-compulsive symptoms when added to therapy with antidepressants,[186-188] although controlled studies have not substantiated these observations,[189] and gabapentin was reported to further reduce OC symptoms when added in an open-label manner to ongoing fluoxetine (30-100 mg/day) treatment in five OCD patients.[190] ❑

REFERENCES

1. Oakley-Browne MA. The epidemiology of anxiety disorders. *Int Rev Psychiatry*. 1991;3:243-252.
2. Robbins N, Regier DA. *Psychiatric Disorder in America: the Epidemiologic Catchment Area study*. New York, NY: Library of Congress Cataloging-in-Publication Data; 1991.
3. Markowitz JS, Weissman MM, Ouellette R, Lish JD, Klermanm GL. Quality of life in panic disorder. *Arch Gen Psychiatry*. 1989;46:984-992.
4. Klerman GL, Weissman MM, Ouellette R, Johnson J, Greenwald S. Panic attacks in the community. Social morbidity and health care utilization. *JAMA*. 1991;265:742-746.
5. Greenblatt DJ, Shader RI. Drug therapy. Benzodiazepines. *N Engl J Med*. 1974;291:1011-1015.
6. Greenblatt DJ, Shader RI. Drug therapy. Benzodiazepines. *N Engl J Med*. 1974;291:1239-1243.
7. Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy: current status of benzodiazepines. Part One. *N Engl J Med*. 1983;309:354-358.
8. Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy: current status of benzodiazepines. Part Two. *N Engl J Med*. 1983;309:410-416.
9. Rickels K, Downing R, Schweitzer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry*. 1993;50:884-895.
10. Rickels K, Weisman K, Norstad N, et al. Buspirone and diazepam in anxiety: a controlled study. *J Clin Psychiatry*. 1982;43:81-86.
11. Rosenbaum JE, Woods SW, Groves JE, et al. Emergence of hostility during alprazolam treatment. *Am J Psychiatry*. 1984;141:792-793.
12. Hoehn-Saric R, McLeod DR, Zimmerli WD. Differential effects of alprazolam and imipramine in generalized anxiety disorder: somatic versus psychic symptoms. *J Clin Psychiatry*. 1988;49:293-301.
13. Davidson JR. Pharmacology of generalized anxiety disorder. *J Clin Psychiatry*. 2001;62(suppl 11):46-50.
14. Rickels K, Case WG, Downing RW, et al. Long-term diazepam therapy and clinical outcome. *JAMA*. 1983;250:767-771.
15. Rickels K, Fox IL, Greenblatt DJ, et al. Clorazepate and lorazepam: clinical improvement and rebound anxiety. *Am J Psychiatry*. 1988;145:312-317.
16. Rickels K, Schweitzer E, Csanalosi I, et al. Long-term treatment of anxiety and risk of withdrawal: prospective comparison of clorazepate and buspirone. *Arch Gen Psychiatry*. 1988;45:444-450.
17. Schweitzer E, Rickels K. Pharmacological treatment for generalized anxiety disorder. In: Mavissakalian MR, Prien RF, eds. *Long-Term Treatments of Anxiety Disorders*. Washington, DC: American Psychiatric Press; 1996:201-220.
18. Blazer DG, Hughes DC, George LK, Swartz M, Boyar J. Generalized anxiety disorder. In: Bobus LN, Regier DA, eds. *Psychiatric Disorders in America: The Epidemiological Catchment Area Study*. New York, NY: Fress Press; 1991:180-203.
19. Rickels K, Schweizer E. Benzodiazepines for the treatment of panic attacks: a new look. *Psychopharmacol Bull*. 1986;22:93-99.
20. Kastenholz KV. Buspirone, a novel nonbenzodiazepine anxiolytic. *Clin Pharmacol*. 1984;3:600-607.
21. Cohn JB, Bowden CL, Fisher JG, et al. Double-blind comparison of buspirone and clorazepate in anxious outpatients. *Am J Med*. 1986;80(suppl 3b):10-16.
22. Sussman N. Treatment of anxiety with buspirone. *Psychiatr Ann*. 1987;17:114-120.
23. Rickels K, Amsterdam J, Clary C, et al. Buspirone in major depression: a controlled study. *J Clin Psychiatry*. 1991;52:34-38.
24. Schweitzer E, Rickels K. Buspirone in the treatment of panic disorder: a controlled pilot comparison with clorazepate. *J Clin Psychopharmacol*. 1988;8:803.
25. Sheehan D, Raj AB, Sheehan KH, et al. Is buspirone effective for panic disorder? *J Clin Psychopharmacol*. 1990;10:3-11.
26. Delle Chiaie R, Pancheri P, Casacchia M, Stratta P, Kotzalidis GD, Zibellini M. Assessment of the efficacy of buspirone in patients affected by generalised anxiety disorder, shifting to buspirone from prior treatment with lorazepam: a placebo-controlled, double-blind study. *J Clin Psychopharmacol*. 1995;15:12-19.
27. Csanalosi I, Schweizer E, Case WG, et al. Gepirone in anxiety: a pilot study. *J Clin Psychopharmacol*. 1987;7:31-33.
28. Rickels K, Schweizer E, De Martinis M, Mandos L, Mercer C. Gepirone and diazepam in generalised anxiety disorders: a placebo-controlled trial. *J Clin Psychopharmacol*. 1997;17:272-277.
29. Borison RL, Albrecht JW, Diamond L. Efficacy and safety of a putative anxiolytic agent: ipsapirone. *Psychopharmacol Bull*. 1990;26:207-210.
30. Schweizer E, Rickels K. Placebo response in generalized anxiety: its effects on the outcome of clinical trials. *J Clin Psychiatry*. 1997;58(suppl 11):30-38.
31. Johnstone EC, Cunningham Owens DG, Frith CD, et al. Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychol Med*. 1980;10:321-328.
32. Kahn RJ, McNair DM, Lipman RS, et al. Imipramine and chlordiazepoxide in depressive and anxiety disorders. *Arch Gen Psychiatry*. 1986;43:79-85.
33. Hedges DW, Reimherr FW, Strong RE, et al. An open trial of nefazodone in adult patients with generalized anxiety disorder. *Psychopharmacol Bull*. 1996;32:671-676.
34. Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. *Acta Psychiatr Scand*. 1997;95:444-450.
35. Haskins JT, Aguiar L, Pallay A, Rudolph R. Double-blind, placebo-controlled study of once daily venlafaxine XR (V-XR) in outpatients with generalized anxiety disorder. Presented at the Annual Meeting, Anxiety Disorders Association of America, San Diego, Calif, March 1999.

Psicofarmacología de los trastornos de ansiedad

La población general se expone a un riesgo de vida de 1:4 para la ansiedad incapacitante, lo que ha inspirado a generaciones de psicofarmacólogos básicos y clínicos, desde la época de las primeras benzodiazepinas (BZ) hasta la de los inhibidores selectivos de la recaptación de serotonina (ISRS) y compuestos relacionados, por ejemplo, los inhibidores de la recaptación de serotonina y de noradrenalina (IRSN). Este extenso y práctico artículo de revisión resume la investigación terapéutica actual a través del espectro de los trastornos individuales: trastorno de ansiedad generalizada (TAG), trastorno de pánico (TP) y agorafobia (trastorno de ansiedad social), trastorno compulsivo (TOC), trastorno fóbico (incluyendo la fobia social) y el trastorno por estrés postraumático (TEPT). El diagnóstico específico es una condición previa para una terapia exitosa: a pesar de una considerable sobreposición, cada trastorno responde de preferencia a una terapia farmacológica específica. La comorbilidad con la depresión es frecuente; de ahí el éxito de los ISRS, los cuales fueron originalmente diseñados para tratar la depresión. La evaluación sigue siendo un problema (mediciones multivariadas versus puntuación final individual), al igual que – con frecuencia – evaluar la eficacia y la tolerancia. El ansiolítico ideal sigue siendo el "Santo Grial" de la investigación psicofarmacológica mundial.

Psychopharmacologie des troubles anxieux

Dans la population générale, l'exposition au risque d'anxiété invalidante est de 1/4 au cours de la vie; ceci a inspiré des générations de psychopharmacologues fondamentalistes et cliniques, de l'ère des premières benzodiazépines (BZ) à celle des inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) et autres composés apparentés, par ex. la sérotonine et les inhibiteurs de la recapture de la noradrénaline (IRN). La présente analyse pratique résume de façon exhaustive la recherche thérapeutique actuelle à travers un éventail de troubles tels que : anxiété généralisée (TAG), trouble panique (TP) et agoraphobie (trouble anxieux social), trouble compulsif (TOC), névrose phobique (y compris la phobie sociale), et névrose de stress posttraumatique (TSPT). Un diagnostic spécifique est le prérequis d'un traitement efficace : en dépit des intrications importantes, chaque trouble répond de façon préférentielle à une pharmacothérapie spécifique. La comorbidité avec la dépression est fréquente ; d'où le succès des ISRS, qui étaient au départ conçus pour le traitement de la dépression. L'évaluation (mesures dans plusieurs domaines versus *critères individuels) reste problématique, comme le sont - souvent - l'efficacité et la tolérance. L'anxiolytique idéal demeure la quête du Graal de la recherche psychopharmacologique mondiale.*

36. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalised anxiety disorder. *Am J Psychiatry*. 2000;157:968-974.

37. Haskins JT, Rudolph R, Aguiar L, Entsuah R. Double-blind, placebo-comparator–controlled study of once-daily venlafaxine XR (V-XR) and buspirone (Bsp) in outpatients with generalized anxiety disorder (GAD). Presented at the Meeting of the European College of Neuropsychopharmacology, Paris, France, October-November 1998.

38. Haskins JT, Rudolph R, Aguiar L, Entsuah R. Double-blind, placebo-/comparator-controlled study of once daily venlafaxine XR (V-XR) and buspirone (Bsp) in outpatients with generalized anxiety disorder (GAD). Presented at the Annual Meeting of the Anxiety Disorders Association of America, San Diego, Calif, March 1999.

39. Davidson JRT, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalised anxiety disorder. *J Clin Psychiatry*. 1999;60:528-535.

40. Nutt DJ, Argyropoulos SV, Forshall S. In: *Generalized Anxiety Disorder: Diagnosis, Treatment and its Relationship to Other Anxiety Disorders*. London, UK: Martin Dunitz; 1998:63-77.

41. Ballenger JC, McDonald S, Noyes R, et al. The first double-blind, placebo-controlled trial of a partial benzodiazepine agonist abecarnil in generalized anxiety disorder. *Psychopharmacol Bull*. 1991;27:171-179.

42. Lydiard RB, Ballenger JC, Rickels K for the Abecarnil Work Group. A double-blind evaluation of the safety and efficacy of abecarnil, alprazolam, and placebo in outpatients with generalized anxiety disorder. *J Clin Psychiatry*. 1997;58(suppl 11):11-18.

43. Pollack MH, Worthington JJ, Manfro, GG, et al. Abecarnil for the treatment of generalized anxiety disorder: a placebo-controlled comparison of two dosage ranges of abecarnil and buspirone. *J Clin Psychiatry*. 1997;58(suppl 11):19-23.

44. Barranco SF, Bridger W. Treatment of anxiety with oral hydroxyzine: an overview. *Curr Ther Res*. 1977;22:217-227.

45. Ferreri M, Hantouche EG. Recent clinical trials of hydroxyzine in generalised anxiety disorder. *Acta Psychiatr Scand Suppl*. 1998;393:102-108.

46. Hayes PE, Schulz SC. Beta-blockers in anxiety disorders. *J Affect Disord*. 1987;13:119-130.

47. Boerner RJ. Kava kava in the treatment of generalized anxiety disorder, simple phobia and specific social phobia. *Phytother Res*. 2001;15:646-647.

48. Abadi S, Papoushek C, Evans MF. Is kava extract effective for treating anxiety? *Can Fam Physician*. 2001;47:1745-1747.

49. Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther*. 2001;26:363-367.

50. Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I. Efficacy in short-term treatment. *Arch Gen Psychiatry*. 1988;45:413-422.
51. Andersch JC, Rosenberg NK, Kullingsjo H. Efficacy and safety of alprazolam, imipramine and placebo in the treatment of panic disorder. A Scandinavian multicentre study. *Acta Psychiatr Scand*. 1991;365(suppl):18-27.
52. Schweizer E, Rickels K, Weiss S, Zavodnick S. Maintenance drug treatment for panic disorder: II. Short- and long-term outcome after drug taper. *Arch Gen Psychiatry*. 1993;50:61-68.
53. Chouinard G, Labonte A, Fontaine R. New concepts in benzodiazepine therapy: rebound anxiety and new indications for the more potent benzodiazepines. *Prog Neuropsychopharmacol Biol Psychiatry*. 1983;7:669-673.
54. Nagy LM, Krystal JH, Woods SW, Charney DS. Clinical and medication outcome after short-term alprazolam and behavioral group. *Arch Gen Psychiatry*. 1989;46:993-999.
55. Lesser IM, Rubin RT, Rifkin A, et al. Secondary depression in panic disorder and agoraphobia. Dimensions of depressive symptomatology and their response to treatment. *J Affect Disord*. 1989;16:49-58.
56. Cox B, Endler NS, Lee PS, Swinson RP. A meta-analysis of treatments of panic disorder with agoraphobia: imipramine, alprazolam, and in vivo exposure. *J Behav Ther Exp Psychiatry*. 1992;23:175-182.
57. Clum GA, Clum GA, Surls R. A meta-analysis of treatments for panic disorder. *J Consult Clin Psychol*. 1993;61:317-326.
58. Van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. *J Nerv Ment Disord*. 1997;185:510-516.
59. Klein DF, Fink M. Psychiatric reaction patterns to imipramine. *Am J Psychiatry*. 1962;119:432-438.
60. Sargant W, Dally P. Treatment of anxiety states by antidepressant drugs. *BMJ*. 1962;1:6-9.
61. Ballenger JC, Lydiard RB, Turner SM. Panic disorder and agoraphobia. In: Gabbard GO, ed. *Treatments of Psychiatric Disorders Vol 2*. 2nd ed. Washington, DC: American Psychiatric Press; 1997:1421-1452.
62. Ballenger JC. Selective serotonin reuptake inhibitors (SSRIs) in panic disorder. In: Nutt DJ, Ballenger JC, Lepine J-P, eds. *Panic Disorder. Clinical Diagnosis, Management and Mechanisms*. London, UK: Martin Dunitz; 1999:159-178.
63. Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry*. 2001;158:1989-1992.
64. Shear MK, Brown TA, Barlow DH, et al. Multicenter collaborative panic disorder severity scale. *Am J Psychiatry*. 1997;154:1571-1575.
65. Den Boer JA. Pharmacotherapy of panic disorder: differential efficacy from a clinical viewpoint. *J Clin Psychiatry*. 1998;59(suppl 8):30-36.
66. Cross National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine and placebo. *Br J Psychiatry*. 1993;160:191-202.
67. Lecrubier Y, Judge R. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators. *Acta Psychiatr Scand*. 1997;95:153-160.
68. Roy-Byrne PP, Cowley DS. Course and outcome in panic disorder: a review of recent follow-up studies. *Anxiety*. 1995;1:151-160.
69. Marchesi C, Ampollini P, Signifredi R, Maggini C. The treatment of panic disorder in a clinical setting: a 12-month naturalistic study. *Neuropsychobiology*. 1997;36:25-31.
70. Ballenger JC. Medication discontinuation in panic disorder. *J Clin Psychiatry*. 1992;53S:26-31.
71. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Baldwin DS, den Boer JA. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry*. 1998;59(suppl 8):47-54.
72. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder. A double-blind multicenter trial. *Am J Psychiatry.* 1998;155:1189-1195.
73. Tiller JW, Bouwer C, Behnke K. Moclobemide for anxiety disorders: a focus on moclobemide for panic disorder. *Int Clin Psychopharmacol*. 1997;12(suppl 6):s27-s30.
74. Loerch B, Graf-Morgenstern M, Hautzinger M, et al. Randomised placebo-controlled trial of moclobemide, cognitive-behavioral therapy and their combination in panic disorder with agoraphobia. *Br J Psychiatry*. 1999;174:205-212.
75. Geracioti TD. Venlafaxine treatment of panic disorder: a case series. *J Clin Psychiatry*. 1995;56:408-410.
76. Boshuisen ML, Slaap BR, Vester-Blokland ED, den Boer JA. The effect of mirtazapine in panic disorder: an open-label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol*. 2001;16:363-368.
77. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. *Braz J Med Biol Res*. 2001;34:1303-1307.
78. Versiani M, Cassano GB, Perugi G, et al. Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry*. 2002;63:31-37.
79. Sheehan DV, Raj AB, Harnett-Sheehan K, Soto S, Knapp E. The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: a double-blind placebo-controlled study. *Acta Psychiatr Scand*. 1993;88:1-11.
80. Sandford JJ, Forshall S, Bell C, et al. Crossover trial of pagoclone and placebo in patients with *DSM-IV* panic disorder. *J Psychopharmacol*. 2001;15:205-208.
81. Munjack DJ, Crocker B, Cabe D, et al. Alprazolam, propranolol, and placebo in the treatment of panic disorder and agoraphobia with panic attacks. *J Clin Psychopharmacol*. 1989;9:22-27.
82. Layton ME, Friedman SD, Dager SR. Brain metabolic changes during lactate-induced panic: effects of gabapentin treatment. *Depress Anxiety*. 2001;14:251-254.
83. Laufer N, Weizman A. Other drug treatments and augmentation therapies for panic disorder. In: Nutt, DJ, Ballenger, JC, Lepine, J-P, eds. *Panic Disorder. Clinical Diagnosis, Management and Mechanisms*. London, UK: Martin Dunitz; 1999:179-202.
84. Balon R, Ramesh C. Calcium channel blockers for anxiety disorders? *Ann Clin Psychiatry*. 1996;8:215-220.
85. Davidson JRT, Potts N, Richichi E, Krishnan R, Ford SM, Smith R. Treatment of social phobia with clonazepam and placebo. *J Clin Psychopharmacol*. 1993;13:423-428.
86. Gelernter CS, Uhde TW, Cimbolic P, et al. Cognitive-behavioral and pharmacological treatments for social phobia. A controlled study. *Arch Gen Psychiatry*. 1991;48:938-945.
87. Versiani M, Nardi AE, Figueira I, Mendlowicz M, Marques C. Double-blind placebo-controlled trial with bromazepam in social phobia. *J Brasil Psiquiatria*. 1997;46:167-171.
88. Van Vliet M, Den Boer JA, Westenberg HG. Psychopharmacological treatment of social phobia: a double-blind, placebo-controlled study with fluvoxamine. *Psychopharmacol (Berl)*. 1994;115:128-134.
89. Pollack MH, Gould RA. The pharmacotherapy of social phobia. *Int Clin Psychopharmacol*. 1996;11(suppl 3):71-75.
90. Liebowitz MR, Schneier F, Campeas R, Hollander E. Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. *Arch Gen Psychiatry*. 1992;49:290-300.
91. Versiani M, Nardi AE, Mundim FD, Alves AB, Leibowitz MR, Amrein R. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. *Br J Psychiatry*. 1992;161:353-360.
92. Heimberg RG, Liebowitz MR, Hope DA, et al. Cognitive-behavioral group therapy versus phenelzine in social phobia: 12-week outcome. *Arch Gen Psychiatry*. 1998;55:1133-1141.
93. Van Vliet M, Den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO-A inhibitor. *Eur Psychopharmacol*. 1992;2:21-29.
94. Fahlen T, Nilsson HL, Borg K, Humble M, Pauli U. Social phobia: the clinical efficacy and tolerability of the monoamine oxidase-A and serotonin uptake inhibitor brofaromine. A double-blind, placebo-controlled study. *Acta Psychiatr Scand*. 1995;92:351-358.
95. Lott M, Greist JH, Jefferson JW, et al. Brofaromine for social phobia: a multicenter, placebo-controlled, double-blind study. *J Clin Psychopharmacol*. 1997;17:255-260.

96. Katschnig H, Stein M, Buller R (on behalf of the International Multicenter Clinical Trial Group on Moclobemide in Social Phobia). Moclobemide in social phobia: a double-blind, placebo-controlled clinical study. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:71-80.
97. Noyes R Jr, Moroz G, Davidson JRT, et al. Moclobemide in social phobia: a controlled-dose response trial. *J Clin Psychopharmacol*. 1997;17:247-254.
98. Schneier FR, Goetz D, Campeas R, Fallon B, Marshall R, Liebowitz MR. Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry*. 1998;172:70-77.
99. Stein MB, Liebowitz MR, Lydiard RB, Pitts CD, Bushnell W, Gergel I. Paroxetine treatment of generalized social phobia (social anxiety disorder): A randomized controlled trial. *JAMA*. 1998;280:708-713.
100. Stein DJ, Stein MB, Goodwin W, Kumar R, Hunter B. The selective serotonin reuptake inhibitor paroxetine is effective in more generalized and in less generalized social anxiety disorder. *Psychopharmacology (Berl)*. 2001;158:267-272.
101. Stein DJ, Stein MB, Pitts CD, Kumar R, Hunter B. Predictors of response to pharmacotherapy in social anxiety disorder: an analysis of 3 placebo-controlled paroxetine trials. *J Clin Psychiatry*. 2002;63:152-155.
102. Baldwin D, Bobes J, Stein DJ, Scharwachter I, Faure M. Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. Paroxetine Study Group. *Br J Psychiatry*. 1999;175:120-126.
103. Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. *Acta Psychiatr Scand*. 1999;100:193-198.
104. Stein MB, Fyer AJ, Davidson JRT, Pollack MH, Wiita B. Fluvoxamine treatment so social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *Am J Psychiatry*. 1999;156:756-760.
105. Katzelnick DJ, Kobak KA, Greist JH, Jefferson JW, Mantle JM, Serlin RC. Sertraline for social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry*. 1995;152:1368-1371.
106. Van Ameringen MA, Lane RM, Walker JR, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158:275-281.
107. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. *J Clin Psychiatry*. 1993;54:27-32.
108. Kelsey JE. Venlafaxine in social phobia. *Psychopharmacol Bull*. 1995;31:767-771.
109. Van Ameringen MV, Mancini C, Oakman JM. Nefazodone in social phobia. *J Clin Psychiatry*. 1999;60:96-100.
110. Bouwer C, Stein CJ. Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. *J Affect Disord*. 1998;49:79-82.
111. Simon NM, Sharma SG, Worthington JJ, Marzol PC, Pollack MH. Citalopram for social phobia: a clinical case series. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001;25:1469-1474.
112. Varia IM, Cloutier CA, Doraiswamy PM. Treatment of social anxiety disorder with citalopram. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:205-208.
113. Emmanuel NP, Lydiard RB, Ballenger JC. Treatment of social phobia with bupropion. *J Clin Psychopharmacol*. 1991;11:276-277.
114. Schneier FR, Franklin R, Saoud JB, et al. Buspirone in social phobia. *J Clin Psychopharmacol*. 1993;13:251-256.
115. Munjack DJ, Bruns J, Baltazar PL, et al. A pilot study of buspirone in the treatment of social phobia. *J Anxiety Disord*. 1991;5:87-98.
116. Van Ameringen, M, Mancini, C, Wilson, C. Buspirone augmentation of selective serotonin reuptake inhibitors (SSRIs) in social phobia. *J Affect Disord*. 1996;39:115-121.
117. Van Vliet IM, Den Boer JA, Westenberg HGM, Pian KLH. Clinical effects of buspirone in social phobia: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 1997;58:164-168.
118. Turner SM, Beidel DC, Jacob RG. Social phobia: a comparison of behavior therapy and atenolol. *J Consult Clin Psychol*. 1994;62:350-358.
119. Stein MB, Sareen J, Hami S, Chao J. Pindolol potentiation of paroxetine for generalized social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry*. 2001;158:1725-1727.
120. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol*. 1999;19:341-348.
121. Selak I. Pregabalin (Pfizer). *Curr Opin Invest Drugs*. 2001;2:828-834.
122. Braun P, Greenberg D, Dasberg H. Core symptoms of post-traumatic stress disorder un-improved by alprazolam treatment. *J Clin Psychiatry*. 1990;51:236-238.
123. Friedman MJ. Current and future drug treatment for posttraumatic stress disorder patients. *Psychiatry Ann*. 1998;28:461-468.
124. O'Brien M, Nutt DJ. Loss of consciousness and post-traumatic stress disorder. *Br J Psychiatry*. 1998;173:102-104.
125. Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. *J Clin Psychiatry*. 1996;57:390-394.
126. Frank JB, Kosten TR, Giller EL, Dan E. A randomized clinical trial of phenelzine and imipramine for post-traumatic stress disorder. *Am J Psychiatry*. 1988;145:1289-1291.
127. Kosten TR, Frank JB, Dan E, McDougle CJ, Giller Jr EL. Pharmacotherapy for post-traumatic stress disorder using phenelzine or imipramine. *J Nerv Ment Dis*. 1991;179:366-370.
128. Davidson JRT, Kudler HS, Saunders WB, et al. Predicting response to amitriptyline in post-traumatic stress disorder. *Am J Psychiatry*. 1993;150:1024-1029.
129. Reist C, Kauffmann CD, Haier RJ, et al. A controlled trial of desipramine in 18 men with post-traumatic stress disorder. *Am J Psychiatry*. 1989;146:513-516.
130. Shestatzky M, Greenberg D, Lerer B. A controlled trial of phenelzine in posttraumatic stress disorder. *Psychiatry Res*. 1988;24:149-155.
131. Neal LA, Shapland W, Fox C. An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol*. 1997;12:231-237.
132. McDougle CJ, Southwick SM, Charney DS, St James RL. An open trial of fluoxetine in the treatment of post-traumatic stress disorder. *J Clin Psychopharmacol*. 1991;11:325-327.
133. Nagy LN, Morgan CA, Southwick SM, Charney DS. Open prospective trial of fluoxetine for post-traumatic stress disorder. *J Clin Psychopharmacol*. 1993;13:107-113.
134. Van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in post traumatic stress disorder. *J Clin Psychiatry*. 1994;55:517-522.
135. Penava SJ, Otto MW, Pollack MH, Rosenbaum JF. Current status of pharmacotherapy for PTSD: an effect size analysis of controlled studies. *Depress Anxiety*. 1997;4:240-242.
136. Kline NA, Dow BM, Brown SA, Matloff JL. Sertraline efficacy in depressed combat veterans with post-traumatic stress disorder. *Am J Psychiatry*. 1994;151:621.
137. Rapaport MH, Endicott J, Clary CM. Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. *J Clin Psychiatry*. 2002;63:59-65.
138. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158:1974-1981.
139. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry*. 2001;158:1982-1988.
140. Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62:860-868.
141. Davidson JRT, Weisler RH, Malik ML, Connor KM. Treatment of posttraumatic stress disorder with nefazodone. *Int Clin Psychopharmacol*. 1998;13:111-113.
142. Hertzberg MA, Feldman ME, Beckham JC, Moore SD, Davidson JRT. Open trial of nefazodone for combat-related posttraumatic stress disorder. *J Clin Psychiatry*. 1998;59:460-464.
143. Lipper S, Davidson JR, Grady TA, et al. Preliminary study of carbamazepine in post-traumatic stress disorder. *Psychosomatics*. 1986;27:849-854.
144. Davidson JRT. Drug therapy of post-traumatic stress disorder. *Br J Psychiatry*. 1992;160:309-314.
145. Kitchner I, Greenstein R. Low dose lithium carbonate in the treatment of posttraumatic stress disorder. *Mil Med*. 1985;150:378-381.
146. Keck Jr PE, McLeroy SL, Friedman LM. Valoprate and carbamazepine in the treatment of panic and posttraumatic stress disorders, withdrawal states, and behavioral dyscontrol syndromes. Review. *J Clin Psychopharmacol*. 1992;12(suppl 1):36S-41S.

147. Petty F, Davis LL, Nugent AL, et al. Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22:100-101.
148. Sutherland SM, Davidson JR. Pharmacotherapy for post-traumatic stress disorder. *Psychiatr Clin North Am*. 1994;17:409-423.
149. Berlant J, van K. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry*. 2002;63:15-20.
150. Hamner MB, Brodrick PS, Labbate LA. Gabapentin in PTSD: a retrospective, clinical series of adjunctive therapy. *Ann Clin Psychiatry*. 2001;13:141-146.
151. Wells BG, Chu CC, Johnson R, et al. Buspirone in the treatment of post-traumatic stress disorder. *Pharmacotherapy*. 1991;11:340-343.
152. Petty F, Brannan S, Casada J, et al. Olanzapine treatment for post-traumatic stress disorder: an open-label study. *Int Clin Psychopharmacol*. 2001;16:331-337.
153. Kolb LC, Burris BC, Griffiths S. Propranolol and clonidine in the treatment of post-traumatic stress disorder of war. In: van der Kolk BA, ed. *Post-traumatic Stress Disorder: Psychological and Biological Sequelae*. Washington, DC: American Psychiatric Press; 1984:98-107.
154. Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol Psychiatry*. 2002;15:189-192.
155. Taylor F, Raskind MA. The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22:82-85.
156. Hewlett WA, Vinogradov S, Agras WS. Clomipramine, clonazepam, and clonidine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:420-430.
157. Clomipramine Collaborative Study Group. Clomipramine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1991;48:730-737.
158. Lydiard RB, Brawman-Mintzer O, Ballenger JC. Recent developments in the psychopharmacology of anxiety disorders. *J Consult Clin Psychol*. 1996;64:660-668.
159. Zohar J, Chopra M, Sasson Y, et al. Psychopharmacology of obsessive-compulsive disorder? *World J Biol Psychiatry*. 2000;1:92-100.
160. Piccinelli M, Pini S, Bellantuono C, et al. Efficacy of drug treatment in obsessive-compulsive disorder. *Br J Psychiatry*. 1995;166:424-443.
161. Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: a meta-analysis. *Arch Gen Psychiatry*. 1995;52:53-60.
162. Piggott TA, Pato MT, Bernstein S, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive compulsive disorder. *Arch Gen Psychiatry*. 1990;47:926-932.
163. Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD Paroxetine Study Investigators. *Br J Psychiatry*. 1996;169:468-474.
164. Bisserbe JC, Lane RM, Flament MF, et al. A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. *Eur Psychiatry*. 1997;153:1450-1454.
165. Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. *Psychopharmacology*. 1997;136:205-216.
166. Mundo, E, Bianchi, L, Bellodi, L. Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. *J Clin Psychopharmacol*. 1997;17:267-271.
167. Greist JH, Jefferson JW, Kobak KA, et al. A one-year, double-blind, placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1995;10:57-65.
168. Pato MT, Zohar-Kadouch R, Zohar J, Murphy DL. Return of symptoms after discontinuation of clomipramine in patients with obsessive compulsive disorder. *Am J Psychiatry*. 1988;145:1521-1525.
169. Rasmussen S, Hackett E, DuBoff E, et al. A 2-year study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1997;12:309-316.
170. Steiner M. Long-term treatment and prevention of relapse in OCD with paroxetine. Presented at the Annual Meeting of the American Psychiatric Association, Miami, Fla, May 1995.
171. McDougle CJ, Goodman WK, Leckman JF, et al. The psychopharmacology of obsessive-compulsive disorder: implications for treatment and pathogenesis. *Psychiatr Clin North Am*. 1993;16:749-766.
172. Jenike MA, Rauch SL. Managing the patient with treatment-resistant obsessive compulsive disorder: current strategies. *J Clin Psychiatry*. 1994;55(suppl 3):11-17.
173. McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH. Haloperidol addition in fluvoxamine-refractory obsessive compulsive disorder. *Arch Gen Psychiatry*. 1994;51:302-308.
174. McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor–refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:794-801.
175. Pfanner C, Marazziti D, Dell'Osso L, et al. Risperidone augmentation in refractory obsessive-compulsive disorder: an open-label study. *Int Clin Psychopharmacol*. 2000;15:297-301.
176. Koran LM, Ringold AL, Elliott MA. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2000;61:514-517.
177. Mohr N, Vythilingum B, Emsley RA, Stein DJ. Quetiapine augmentation of serotonin reuptake inhibitors in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2002;17:37-40.
178. Koran LM, Sallee FR, Pallanti S. Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:396-401.
179. Fallon BA, Liebowitz MR, Campeas R, et al. Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry*. 1998;55:918-924.
180. Vallejo J, Olivares J, Marcos T, Bulbena A, Menchon JM. Clomipramine versus phenelzine in obsessive-compulsive disorder. A controlled clinical trial. *Br J Psychiatry*. 1992;161:665-670.
181. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:1261-1264.
182. Pato MT, Pigott TA, Hill JL, Grover GN, Bernstein SE, Murphy DL. Controlled comparison of buspirone and clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1991;148:127-129.
183. Piggott TA, L'Heureux F, Hill JL, Bihari K, Bernstein SE, Murphy DL. A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:11-18.
184. Grady TA, Pigott TA, L'Heureux F, Hill JL, Bernstein SE, Murphy DL. Double-blind study of adjuvant buspirone for fluoxetine-treated patients with obsessive-compulsive disorder. *Am J Psychiatry.* 1993;150:819-821.
185. Fux XM, Levine J, Aviv A, Belmaker RH. Inositol treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 1996;153:1219-1221.
186. Stern TA, Jenike MA. Treatment of obsessive-compulsive disorder with lithium carbonate. *Psychosomatics*. 1983;24:671-673.
187. Rasmussen SA. Lithium and tryptophan augmentation in clomipramine-resistant obsessive-compulsive disorder. *Am J Psychiatry*. 1984;141:1283-1285.
188. Golden RN, Morris JE, Sack DA. Combined lithium-tricyclic treatment of obsessive-compulsive disorder. *Biol Psychiatry*. 1988;23:181-185.
189. McDougle CJ, Price LH, Goodman WK, Charney DS, Heninger GR. A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. *J Clin Psychopharmacol*. 1991;11:175-184.
190. Cora-Locatelli G, Greenberg BD, Martin J, Murphy DL. Gabapentin augmentation for fluoxetine-treated patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 1998;59:480-481.

Childhood predictors of states of anxiety

Jerome Kagan, PhD

Development of the characteristics of social phobia often requires a diathesis in the form of a temperamental bias. A behavioral profile marked by vigorous motor activity and crying to unfamiliar stimuli at 4 months of age—called high reactivity—is characteristic of about 20% of healthy, Caucasian infants. This pattern predicts shy behavior in preschool children and symptoms of social anxiety at age 7, and, at age 11, a subdued personality and biological features that are consonant with a hypothesis of amygdalar excitability. The biological variables that best characterize the children who had been high-reactive infants are right-hemisphere activity in the electroencephalogram (EEG), a larger evoked potential from the inferior colliculus, higher sympathetic tone in the cardiovascular system, and larger event-related potentials to discrepant stimuli. About a quarter of 11-year-olds who had been high reactives displayed behavioral and biological characteristics that are in theoretical accord with the hypothesis of amygdalar excitability, while only 1 of 20 displayed a profile characterized by features in opposition to their temperament. The evidence points to a modest temperamental contribution to the development of symptoms currently regarded as diagnostic of social phobia.

Dialogues Clin Neurosci. 2002;4:287-293.

There is now a consensus that chronic possession of any one of the categories of anxiety disorder is most likely for individuals who inherit a temperamental diathesis.[1] The evidence used to infer a state of anxiety in humans can include verbal report, observed behaviors, or physiology. These three categories of evidence are not highly correlated and, therefore, the meaning of "anxiety" inferred from one source of information is not equivalent to the meaning inferred from a different source. It is important, therefore, to distinguish among four different concepts.[2]

Judged anxiety refers to verbal statements, on questionnaires or interviews, describing tension, uncertainty, or worry. However, had physiological measures been gathered on these individuals, they would not show the expected physiological accompaniments to their verbal statements. *Constructed anxiety* refers to a verbal report of anxiety that is accompanied by a physiological profile, but not the profile scientists assume to be theoretically appropriate. For example, an individual with an infection might feel tense and, in an attempt to understand this feeling tone, might decided that he or she is worried. *Physiological anxiety* refers to activation of the amygdala and its projections in individuals who do not report conscious feelings of anxiety. The fourth construct is the one most clinicians and scientists seek to measure. The individual reports feeling worried, tense, or anxious and, in addition, displays the physiological features that should accompany those feelings, including asymmetry of activation in the electroencephalogram (EEG) or high sympathetic tone.

Some individuals inherit a temperament that renders them especially vulnerable to the latter state of anxiety. This temperamental bias is regarded as a diathesis for the development of one or more of the psychiatric anxiety

Keywords: *temperament; anxiety; social phobia; children*

Author affiliations: Department of Psychology, Harvard University, Cambridge, Mass, USA

Address for correspondence: Jerome Kagan, PhD, Department of Psychology, Harvard University, 33, Kirkland Street, Cambridge, MA 02138, USA
(e-mail: jk@wjh.harvard.edu)

disorders.[3] It is assumed that these temperamental biases are influenced, in part, by heritable variation in the complex neurochemistry of the central and autonomic nervous systems. The relevant neurochemistry could include variation in γ-aminobutyric acid (GABA), corticotropin-releasing hormone, opioids, norepinephrine, and other molecules.[4]

Study design

Evaluation from age 4 months to 7 years

My laboratory has been studying longitudinally a large group of healthy, Caucasian children from middle-class families who have been followed from 4 months to 11 years.[4] Each infant was classified at 4 months of age into one of four temperamental groups based on their behavior to a standard battery of visual, auditory, and olfactory stimuli. Infants who showed a combination of frequent, vigorous motor activity combined with frequent crying were classified as high reactive (22% of the sample). Infants who showed the opposite profile of infrequent motor activity and minimal crying were classified as low reactive (40%). Infants who showed infrequent motor activity, but frequent crying were classified as distressed (25%), and infants who showed frequent motor activity, but minimal distress were classified as aroused (10%). It is assumed, but not yet proven, that the high- and low-reactive groups inherit different profiles of excitability in the amygdala and/or bed nucleus and their projections. These temperamental groups are regarded as categories rather than a continuum of reactivity.

The children from these temperamental groups were evaluated twice in the second year for their reaction to unfamiliar people, situations, and procedures. The 14- and 21-month-old children who had been categorized as high reactive as infants were more likely than the low reactives to display high levels of fear to unfamiliar people, rooms, and events.[4] This relationship has been verified by Fox and colleagues,[5] who also found that 1-year-olds who had been classified as high-reactive infants at 4 months were more fearful than others when they encountered unfamiliar events.

These children were observed when they were four and a half years old in a play session with two other unfamiliar children of the same sex and age, while the three mothers sat on a couch in the playroom. Each child was classified reliably as inhibited, uninhibited, or neither, based on their behavior with the other children and their reactions to two unfamiliar events that occurred after the play session. Significantly more high than low reactives were classified as inhibited. They were quiet, spent long times close to their mother, and did not initiate social interaction with the other children.

When the children were seven and a half years old, we evaluated the prevalence of anxious symptoms in 51 high reactives, 60 low reactives, and 53 children from the other two temperamental groups. The classification of anxious symptoms, which included extreme shyness, worry about the future, fear of thunderstorms, animals, or loud noises, recurrent nightmares, and occasional reluctance to go to school, was based on questionnaire and interview data with the mother and the child's teacher. A total of 43 of the 164 children met criteria for possession of anxious symptoms. Forty-five percent of the children who had been high-reactive infants, compared with 15% of low reactives, had anxious symptoms (chi-square=12.8, $P<0.01$).[6] High reactives who had anxious symptoms were more fearful in the second year and had higher sitting diastolic blood pressures and a greater magnitude of cooling of the temperature of the fingertips across a series of digit recall problems, compared with other high reactives. Cooling of the fingertips is the result of sympathetic inervation of the arteriovenous anastomoses under the surface of the skin.

Evaluation at age 11 years

These children were evaluated most recently when they were 11 years old. The 3-hour battery consisted of both behavioral and biological assessments. The behavioral data included the number of spontaneous comments and smiles displayed toward the examiner during the first 18 min of interaction, a reliable rating (4-point scale) of the degree of uncertainty, tension, and anxiety displayed by the child in this setting, and a maternal Q-sort of 28 items describing the child's behavior.

Four different classes of biological variables, each under the potential influence of the amygdala, were also quantified. These biological variables were: (i) asymmetry in the magnitude of desynchronization of alpha frequencies in the EEG; (ii) magnitude of the evoked potential from the inferior colliculus to a series of clicks; (iii) sympathetic tone in the cardiovascular system; and (iv) the magnitude of the wave form at 400 ms in the event-related potential to discrepant visual scenes.

Most children and adults have less alpha power in the left than in the right frontal area when at rest, suggesting greater activation of cortical pyramidal neurons in the left frontal lobe. Further, individuals with this EEG profile report more sanguine moods and fewer signs of anxiety than the smaller proportion, who show greater activation on the right side.[7] The amygdala sends ipsilateral projections to the frontal lobe through the basal nucleus of Meynert and it is likely that these projections contribute to the asymmetry in the alpha band of the EEG. A child who had greater activation in the right amygdala should show greater desynchronization of alpha frequencies in the right hemisphere and would be classified as right hemisphere active.

The brain stem auditory evoked response (BAER), elicited by a series of clicks delivered through earphones, was a relevant measure because variation in the magnitude or latency of the fifth wave in the BAER response—called "wave 5"—differentiates between personality and clinical categories.[8-11] In addition, adults with panic disorder show a larger wave 5 than do controls.[12] The peak of the fifth wave is believed to represent the termination of the lateral lemniscus on the inferior colliculus.[13] The theoretical relevance of this fact is that the amygdala projects to the inferior colliculus through both the central gray and the locus cereleus and, therefore, children with a more excitable amygdala should display a larger wave 5 than others.[14]

The rationale behind recording the event-related potential to discrepant visual stimuli derived from the assumption that the amygdala reacts to discrepant or unexpected events and projects to cortical neurons that mediate the event-related potential.[15] If high reactives possess a low threshold of reactivity in the amygdala and its projections, then they should show a larger event-related potential to discrepant events. The usual wave form to a discrepant event occurs between 150 and 800 ms with a peak between 300 and 400 ms. Preadolescent children most often show a negative wave form that is called Nc (for negative component).[16]

Each child was presented, through goggles, two series of pictures with 169 pictures in each series. In the first series, 70% of the pictures were of the same item (a fireworks display), 15% were of the same flower, the oddball stimulus, and the remaining 15% were each different, but ecologically valid (a chair or kitchen utensil). These pictures were called novel valid. In the second series, the frequent picture presented 70% of the time was a yellow fire hydrant, the oddball stimulus was a different flower, and the remaining fifteen percent of the pictures were each different, but ecologically invalid (for example, a chair with three legs). These pictures were called novel invalid.

Finally, we recorded measures of cardiovascular activity as an index of reactivity in the sympathetic nervous system. The amygdala sends varied projections to the sympathetic system and, therefore, we assumed that high reactives would show signs of greater sympathetic reactivity than low reactives.[17]

The two major variables were the ratio of high- to low-frequency power in the cardiac spectrum while the child was laying supine. A fast Fourier transformation of the distribution of beat-to-beat differences in the sample of resting heart rate usually reveals two peaks in the distribution. The higher frequency, around 0.2 Hz, represents the parasympathetic influence of respiration on heart rate–vagal tone. The lower frequency band, from 0.02 to 0.10 Hz, represents both sympathetic and parasympathetic influences on heart rate, due to cycles of change in blood pressure and body temperature. Higher relative power in the low frequency band is usually correlated with a high resting heart rate and is indicative of higher sympathetic tone.[18]

Results

Behavior

The high-reactive children were more subdued and anxious at the 11-year evaluation than the low reactives and were rated as more anxious and inhibited during the first 18 min of the interview *(Table I)*.

Rating	Low reactive	High reactive
1 (relaxed, uninhibited)	50%	22%
2	28%	22%
3	8%	22%
4 (maximally anxious, inhibited)	14%	34%

Table I. Percentage of high and low reactives receiving ratings of 1, 2, 3, or 4, while interacting with the examiner at the 11-year-old evaluation.

Twice as many high as low reactives were rated as extremely inhibited (rating of 4; awarded to children who made very few comments and smiles, displayed a great deal of motor tension, spoke in a soft voice, and

showed other signs of concern). Twice as many low as high reactives were rated as minimally anxious and uninhibited with a rating of 1, which described a maximally relaxed and spontaneous child (chi-square=11.8, $P<0.01$). Further, more high than low reactives had values for both number of spontaneous comments and smiles in the lowest quartile of the two distributions; more low reactives had values in the highest quartile for both measures (chi-square=4.2, $P<0.05$). Thus, the infant temperamental profiles predicted, to a modest degree, spontaneity or a subdued style with the unfamiliar adult examiner.

One half of the current group of high and low reactives had been seen when they were four and a half and seven and a half years of age. A similar rating of degree of anxiety/inhibition on a 4-point scale was assigned to each child based on 90 min of interaction with a different, but unfamiliar female examiner. Seventy percent of the low reactives, but only 13% of the high reactives were uninhibited at all three ages; 38% of high reactives, but only 6% of low reactives were inhibited at all three ages (chi-square=21.3, $P<0.001$). It was rare for a low-reactive infant to become a consistently inhibited child or for a high-reactive infant to become a consistently uninhibited child. As expected, the uninhibited profile was better preserved because family and friends encourage sociability and discourage shyness and timidity.

Seven descriptive items on the maternal Q-sort referred to shyness or sociability in the child. We computed the mean ranks the mother assigned to her child for the three shy and the four sociable items. High reactives were described as more shy and less sociable than the low reactives ($t(149)=3.91$, $P<0.01$).

Biological variables

Figure 1 illustrates the mean standard scores for high and low reactives on the four biological variables at 11 years of age: right parietal activation in the EEG, wave 5 magnitudes, sympathetic tone (a low ratio and a high resting heart rate), and the mean of the integrated voltages from 400 to 1000 ms for the event-related potential to the first oddball flower and the novel invalid scenes.

The high reactives had greater EEG activation at the right parietal site ($t(152)=2.53$, $P<0.05$). Further, the high reactives who had been highly fearful in the second year showed greater activation in the right frontal area compared with low reactives who were equally fearful in the

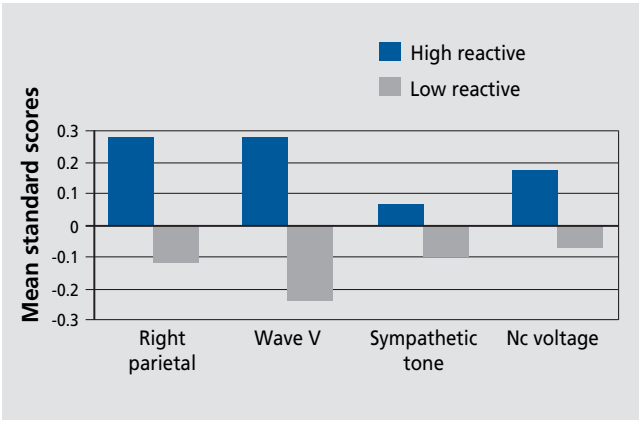


Figure 1. Mean standard score for four biological variables for 11-year-old children who were classified as high or low reactive at 4 months.

second year. The high reactives also had significantly larger wave 5 values ($t(125)=2.87$, $P<0.05$), and this variable best separated the two temperamental groups.[19]

The high reactives also had greater sympathetic tone in the cardiovascular system; 49% of high reactives, but only 32% of low reactives, combined a low ratio in the spectral analysis with a high resting heart rate; 32% of the low reactives, but only 16% of high reactives, combined a high ratio with a low resting heart rate (chi-square=4.9, $P<0.05$). It is also of interest that high sympathetic tone was the best correlate of behavior. The children with high sympathetic tone, compared to those with high vagal tone, spoke less often, were rated as more anxious, and were described by their mother as shy. Although the EEG, wave 5, and event-related potential data also separated the two temperamental groups, these measures were less closely related to the child's behavior.

One explanation is that sympathetic activity is likely to influence the orbitofrontal cortex, which mediates a conscious awareness of feeling tone. A rise in heart rate and blood pressure and a change in breathing results in information being sent to the brain through the medulla to provoke changes in the orbitofrontal cortex that can evoke an alteration in conscious feeling. A subdued mood and avoidance behavior can be consequences of this altered feeling tone. By contrast, activity in the inferior colliculus and the pyramidal neurons of the cortex are less likely to influence orbitofrontal neurons and, therefore, no change in feeling tone occurs and there should be a minimal relationship to behavior. It is important that among high and low reactives, who were equally

subdued in their behavior in the laboratory, only the high reactives showed the biological features of right parietal asymmetry and a large wave 5. The similar behaviors do not necessarily imply similar values on all biological variables. That is why it is important for investigators and clinicians to gather biological data to supplement their behavioral observations and interviews.

Finally, the high reactives had significantly larger Nc voltages to the first oddball picture and the novel invalid pictures ($t(136)=2.00$, $P<0.05$). Further, the correlation between the voltages and these two classes of pictures across frontal and parietal sites were always positive and significant for high-reactive children, but not for the low reactives. That is, only high reactives showed coherence in the magnitude of the Nc across disparate cortical sites, implying that the discrepant scenes recruited neurons over a broader cortical area.

There was an interesting asymmetry in the sensitivity of low compared with high values on the four biological measurements. Low values better differentiated low from high reactives than did high values, suggesting that it is easier for low-reactive than for high-reactive children to attain a state of low cortical and autonomic arousal, even though the former can attain, temporarily, a state of higher arousal in a laboratory setting. All animals must be biologically prepared to become aroused to threat or challenge. The psychological advantages of low arousal are less obvious and apparently a smaller proportion of individuals are able to reach a state of relaxation.

Prediction of states of anxiety

About 1 in 4 children who had been high reactive and 1 in 4 children who had been low reactive developed a behavioral and a biological profile at age 11 that was in accord with theoretical expectations, while only 1 of 20 children developed a profile of social behavior and biology that violated their expected profile. This result is of interest in light of the varied social experiences that these children have encountered over the prior 11 years. Most children displayed behavioral and biological patterns that were characteristic of randomly selected children from middle-class, Caucasian populations. Thus, the prediction that a high-reactive infant will not be highly sociable and exuberant, and show low biological arousal at age 11 can be made with much greater confidence than the prediction that this category of child will be extremely subdued and anxious, and show signs of high arousal in cortical and autonomic targets. The suggestion that a temperamental bias constrains development more effectively than it determines particular outcomes applies to environmental conditions as well. If all one knows about a group of 100 children is that they were born to economically secure, well-educated, nurturing parents and must predict the likely psychological adult outcomes, the most accurate guesses will refer to the profiles that should not occur: criminality, school failure, psychosis, homelessness, drug addiction, and poverty. Predictions concerning the more specific features that will be part of the adult personality are less likely to be validated. Each temperament eliminates many more possibilities than it determines. This principle holds for the cells of the young embryo. The final fate of a neural crest cell in a 3-week-old embryo, whether sensory ganglion, melanocyte, or a muscle of the heart, is less certain than the fact that this cell will definitely not become connective tissue or part of the reproductive system.

Conclusion

The evidence affirms the view that a temperamental bias for high reactivity in infancy, detectable early in development, is predictive of a personality profile marked by shyness, timidity, and anxiety to unfamiliar events and this behavioral phenotype is accompanied by a select biological pattern that implies amygdalar excitability. The question of greater relevance for clinicians is whether this category of child is at higher risk for any of the current psychiatric anxiety disorders. Preliminary evidence invites an affirmative reply. An independent group of 13-year-olds, who had been classified as inhibited or uninhibited in the second year, were interviewed by a psychiatrist who had no knowledge of their initial temperamental classification or later laboratory behavior. More of the adolescents who had been inhibited rather than uninhibited in the second year had symptoms of social anxiety (61% versus 27%).[20] However, these inhibited children were not more likely to have developed specific target phobias or separation anxiety, implying that inhibited children might be at special risk for the development of social phobia during the adolescent or adult years.

The feared target of the social phobic is concern over the evaluations made by unfamiliar people in unfamiliar situations. By contrast, the feared target of the phobic patient is a very specific object that can harm or conta-

minate the agent. The feared target of the panic patient is anxiety over an unexpected autonomic surge. The targets and physiological profiles of these three groups are different and probably comprise different psychiatric categories.

Two puzzles remain. First, 20% of the children were high-reactive infants, but the prevalence of social phobia is less that 10%. This fact suggests that many high reactives find an adaptive niche in their society that allows them to titer unpredictable social encounters. The biography of T. S. Eliot implies that he may have been a high-reactive infant, for he certainly was a shy child. His decision to become a poet permitted a degree of isolation that his temperament required.

The second fact is that more females than males are diagnosed with social phobia, although there is no excess of girls over boys who are classified as high reactive during infancy. This fact suggests that cultural ideals and differential socialization of boys and girls contribute to the sex difference in social phobia. Boys may try much harder to conquer their avoidance behavior and shyness. An excerpt from an essay written by one of the 11-year-old children, who was a high-reactive infant and a fearful toddler supports this claim.

I have always been more of an anxious person than some other people … it took me a very long time to realize how to cope with this heightened state of nervousness … I have also found that the manifestation of my anxiety can be overcome by using simple mind over matter techniques. A good example of this is when I was 8, after learning about what asthma was, I started to feel like I was having trouble breathing. In a heightened state of anxiety, I subconsciously forced myself into believing that I had asthma. This has happened many times. Besides just general fears, it was a struggle to overcome this anxiety manifestation. I overcame these problems, though. I know how to deal with them when they occur. Because I now understand my predisposition towards anxiety, I can talk myself out of simple fears.

It is also important to note that a high-reactive temperament protects the child from engaging in risky behavior—whether drugs, driving at high speeds, or temptations for delinquent behavior. Thus, the child with a high-reactive temperament has some advantages in our society and parents of such infants might decide not to change their child's behavior when the next set of pharmacological advances permits them that choice. ❑

This research was supported by grants from the W. T. Grant Foundation and the Bial Foundation. I thank Nancy Snidman for her continued collaboration.

REFERENCES

1. Regier DA, Narrow WE, Rae BS. The epidemiology of anxiety disorder. *J Psychiatr Res*. 1999;24:3-14.
2. Kagan J, Snidman N, McManis M, Woodward S. Temperamental contributions to the affect family of anxiety. *Psychiatr Clin North Am.* 2001;24:677-688.
3. Torgersen S. Genetic factors in anxiety disorders. *Arch Gen Psychiatry*. 1983;40:1085-1089.
4. Kagan J. *Galen's Prophecy*. New York, NY: Basic Books; 1994.
5. Fox NA, Schmidt LA, Calkins SD. The role of frontal activation in the regulation and dysregulation of social behavior during the preschool years. *Dev Psychopathol*. 1996;80:89-102.
6. Kagan J, Snidman N, Zentner M, Peterson E. Infant temperament and anxious symptoms in school aged children. *Dev Psychopathol*. 1999;11:209-224.
7. Davidson RJ. Anterior electrophysiological asymmetries, emotion, and depression. *Psychophysiology*. 1998;35:607-614.
8. Bullock WA, Gilliland K. Eysenck's arousal theory of introversion-extroversion. *J Pers Soc Psychol*. 1993;64:113-123.
9. Stelmack RM, Wilson KG. Extroversion and the effects of frequency of intensity of the auditory brain stem evoked response. *Pers Individ Dif.* 1982;3:373-380.
10. Swickert RJ, Gilliland K. Relationship between the brain stem auditory evoked response and extroversion, impulsivity, and sociability. *J Res Pers*. 1998;32:314-330.
11. Chiappa KH. *Evoked Potentials in Clinical Medicine*. Philadelphia, Pa: Lippincott-Raven; 1997.
12. Iwanami A, Isono H, Okajima Y, Kamaijima K. Auditory event-related potentials in panic disorder. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:107-111.
13. Amaral DG, Price JL, Pitkanen A, Carmichael ST. *Anatomical Organization of the Primate Amygdaloid Complex in the Amygdala*. New York, NY: Wiley; 1992:1-66.
14. Maisonnette SS, Kawasaki MC, Coimbra NC, Brandao ML. Effects of lesions of amygdaloid nuclei and substantia nigra on aversive responses induced by electrical stimulation of the inferior colliculus. *Brain Res Bull*. 1996;40:93-98.
15. Daffner KR, Scinto LFM, Calvo V, et al. The influence of stimulus deviance on electrophysiologic and behavioral responses to novel events. *J Cog Neurosci*. 2000;12:393-406.
16. de Haan M, Nelson CA. Brain activity differentiates face and object processing in 6-month-old infants. *Dev Psychol*. 1999;35:1113-1121.
17. Le Doux JE, Iwata J, Cicchetti P, et al. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *J Neurosci*. 1988;8:2517-2529.
18. Akselrod S, Gordon D, Ubell FA, Shannon DC, Barger DC, Cohen J. Power spectrum analysis of heart rate fluctuation. *Science*. 1981;213:220-222.
19. Woodward SA, McManis MH, Kagan J, et al. Infant temperament and the brainstem auditory evoked response in later childhood. *Dev Psychol*. 2001;37:1-6.
20. Schwartz CE, Snidman N, Kagan J. Adolescent social anxiety as an outcome of inhibited temperament in childhood. *J Am Acad Child Adolesc Psychiatry*. 1999;38:1008-1015.

Predictores infantiles de los estados de ansiedad

El desarrollo de las características de la fobia social a menudo requiere de una diátesis que se basa en una predisposición del temperamento. Un perfil de conducta marcado por una actividad motora vigorosa y llanto ante estímulos no familiares a los cuatro meses de edad – llamado alta reactividad – es característico en cerca del 20% de los lactantes caucásicos sanos. Este patrón predice una conducta tímida en niños preescolares y síntomas de ansiedad social a la edad de 7 años, y a la edad de 11 años una personalidad reprimida y características biológicas que están en consonancia con una hipótesis de excitabilidad de la amígdala. Las variables biológicas que mejor caracterizan a los niños que han sido lactantes con alta reactividad son una actividad del hemisferio derecho en el electroencefalograma (EEG), un potencial evocado mayor desde el colículo inferior, un tono simpático más elevado en el sistema cardiovascular y mayores potenciales relacionados con eventos para estímulos discrepantes. Cerca de la cuarta parte de los niños de once años que han tenido alta reactividad desarrollan características conductuales y biológicas que están en concordancia teórica con la hipótesis de la excitabilidad de la amígdala, mientras que sólo 1 de 20 desarrolla un perfil caracterizado por rasgos opuestos a su temperamento. La evidencia apunta a una contribución modesta del temperamento al desarrollo de síntomas actualmente considerados en el diagnóstico de la fobia social.

Les facteurs prédictifs des états anxieux de l'enfance

Le développement des traits caractéristiques de la phobie sociale nécessite souvent un terrain à type de déviation du tempérament. Un profil comportemental caractérisé par une réactivité élevée (activité motrice importante et pleurs aux stimuli étrangers) à l'âge de 4 mois se retrouve chez à peu près 20 % des enfants d'origine caucasienne en bonne santé. Un tel schéma est annonciateur d'un comportement timide chez les enfants d'âge préscolaire et de symptômes d'anxiété sociale à l'âge de 7 ans et, à l'âge de 11 ans, d'une personnalité effacée et de caractéristiques biologiques compatibles avec l'hypothèse d'une excitabilité amygdalienne. Les variables biologiques qui caractérisent le mieux les enfants ayant eu une réactivité élevée sont l'activité de l'hémisphère droit sur l'électroencéphalogramme (EEG), un potentiel évoqué du colliculus inférieur augmenté, un tonus sympathique du système cardiovasculaire plus élevé, et des potentiels plus importants aux stimuli contradictoires liés aux événements. Environ un quart des enfants âgés de 11 ans ayant eu une réactivité élevée ont présenté des caractéristiques biologiques et comportementales qui sont en accord théorique avec l'hypothèse d'une excitabilité amygdalienne, tandis que seulement 1 sur 20 a montré un profil caractérisé par des manifestations en opposition avec son tempérament. Cet argument s'inscrit en faveur d'une contribution modeste du tempérament au développement des symptômes considérés actuellement comme permettant de porter le diagnostic de la phobie sociale.

Historical aspects of anxiety

Donald F. Klein, MD

"Anxiety" is a key term for behavioral, psychoanalytic, neuroendocrine, and psychopharmacological observations and theories. Commenting on its historical aspects is difficult, since history is properly a study of primary data. Unfortunately, much clinical anecdote does not correspond to factual records of a long time ago. Even reports of objective studies may suffer from allegiance effects. This essay therefore primarily reflects the personal impact of others' work against the background of my experiences, clinical and scientific. These lead me to question the assumption that "anxiety," as it exists in syndromal disturbances, is simply the quantitative extreme of the normal "anxiety" that occurs during the anticipation of danger. An alternative view that emphasizes dysfunctions of distinct evolved adaptive alarm systems is presented.

Dialogues Clin Neurosci. 2002;4:295-304.

Keywords: *anxiety; panic; fear; history; theory*

Author affiliations: Columbia University, Professor of Psychiatry, New York State Psychiatric Institute, Director of Research, Department of Therapeutics, New York, NY, USA

Address for correspondence: Prof Donald F. Klein, Columbia University, New York State Psychiatric Institute, Department of Therapeutics, 1051 Riverside Drive Unit 22, New York, NY 10032, USA
(e-mail: Donaldk737@aol.com)

I was pleased to be offered the opportunity to contribute a chapter devoted to historical aspects of anxiety. However, my qualifications are clearly not those of a historian, who is properly concerned with documentation derived from primary data.

Primary data consist of documents, records, notes, reports, data, clinical records, hospital charts, church dossiers, tax receipts, artifacts, etc, produced during the historical period in question. Skilled comparative evaluations yield relatively firm inferences, which nevertheless are often controversial and open to "revisionism."

In psychiatry, much early theorizing derives from anecdotal case reports that often, as Freud noted, read like novelistic fiction. Unfortunately, that resemblance is more than superficial. Proper historical studies of primary data have shown that many reports were not only literally fiction in terms of clinical description, but also, more poignantly, in terms of clinical successes that apparently validated innovative therapeutic techniques and novel, insightful theories. Of particular note are the hospital records of Anna O., Freud's actual clinical notes on the "Rat Man," and the Freud–Fliess correspondence. These primary sources stand in stark contradiction to published reports. Further skepticism is warranted by the problematic evidence for "allegiance effects," where an investigator's investments closely parallel their findings. Therefore, critical skepticism is necessary.

My understanding of historical developments derives from two sources—personal experiences and studies—amplified by reading papers and summary accounts at some remove from primary data. This requires an informal essay rather than a detailed footnoted and referenced thesis. Therefore, these historical notes on anxiety are quite personal, emphasizing influences that affected my understanding of that important, ambiguous term. Hopefully, some inferences are justified.

Selected abbreviations and acronyms

CR	*conditioned response*
CS	*conditioned stimulus*
GAD	*generalized anxiety disorder*
PD	*panic disorder*
UR	*unconditioned response*
US	*unconditioned stimulus*

Anxiety

The term "anxiety" is part of common language, referring to common experience, but also refers to pathological states that bear a confusing resemblance to fear and depression (which are also ill-defined lay terms).

A chronological history of the development of ideas about anxiety may give a false impression of continuous cumulative development. As I understand it, different approaches achieved attention in almost direct proportion to the claims of therapeutic efficacy, especially when enhanced by a persuasive explanatory theoretical framework that fits cultural expectations. Rather than cumulative clarification, there is a series of zigzags in perspective.

Descriptions of fear and anxiety were common in classical literature, so that the passions received mythological expressions. The moons of Mars refer appropriately to his sons, the offspring of war, Phobos (fear) and Deimos (flight).

Evolution

The modern era dawned with Darwin, whose exposition of biological evolution through natural selection has recently come to the fore in psychiatric thinking. Darwin's conclusion that emotions were adaptive evolutionary products had been obscured by Freud's Lamarckism, his emphasis on drive and defenses, and his treatment of emotions as epiphenomena.

Since evolutionary theory is more directly informative about function, rather than dysfunction, recent evolutionary theorizing often asserts that many behaviors that are viewed as pathological, eg, mania, psychopathy, agoraphobia, etc, are actually evolved behaviors appropriate to our neolithic ancestors, but discordant with modern times. This viewpoint discounts the starkly minority status of these illnesses, their periodicity, the evidence of brain damage, their response to medication, etc. Such glib formulations obscure the real value of an evolutionary framework for hypothesizing the existence of covert functions that may become impaired, thus producing the syndromes associated with disease.

Cannon

Chronologically, Kraepelin, Pavlov, and Freud should now be in focus, but the direct intellectual descendant of Darwin was in fact Walter Cannon who in 1919 highlighted the emergency adaptive functions of anger and fear in terms of facilitating fight and flight. In strikingly modern terms, he referred to the thalamus as a discrete brain module that provided the integrative connection to the cortex and the sympathoadrenal system, and was therefore the primary instigator of emotional, visceral, and autonomic responses. A narrow focus on adrenergic mechanisms, as the exclusive generator of emergency responses, reemerged recently in attempts to link pathological anxiety to an impaired brain adrenergic system.

Pavlov

Pavlov, who considered himself a physiologist, made the pioneering conditioning observations. Attempts to develop animal models of "neurosis" were initiated when he found that presenting his restrictively harnessed dogs with progressively more difficult discriminations between excitatory and inhibitory conditional stimuli led to frantic agitation (or sometimes sleep). Pavlov also noted the importance of trauma, when a fortuitous kennel flood caused his carefully trained dogs to develop disruptive "neurotic" behaviors. Many drew the conclusion from Pavlov's work that neuroses were learned, since purely experiential procedures caused them. (Pavlov's emphasis on constitutional variation was ignored.)

Learning theory

Behavioral studies led to learning theory, which maintains that anxiety is the conditionable part of fear, serving as a secondary drive. This model, as formulated by Mowrer, seems both simple and powerful. An unconditioned stimulus (US), such as shock, causes unconditioned responses (URs), eg, fear, which leads to escape behavior. Decreases in fear, produced by successful escape, reinforce escape behavior.

Stimuli that regularly precede the US become conditioned stimuli (CSs), which serve as signals of the oncoming US/UR, and release a conditioned response (CR) anxiety, which then becomes a secondary drive inciting avoidant behavior. Successful US avoidance reduces anxiety and thereby reinforces avoidant behavior. Phobic behavior, then, is a learned avoidance maintained by decreases in anxiety. This formulation is still common among learning theorists and behavior therapists.

Certain features of phobias are difficult to reconcile with such a model. What is the US (the shock)? Most phobias do not start with a traumatic incident. Second, why is the range of phobic objects and situations limited? Seligman pointed out that phobias of electric plugs or automobiles should be remarkably common, because many experience shocks from plugs and have to dodge cars, but in fact, such phobias do not exist. The range of phobic objects is limited, often to phylogenetically significant sources of danger. Classic learning theory, however, has no place for especially efficacious evolved CSs. Currently, there is debate on whether such stimuli (eg, heights) directly engender fear or facilitate conditioning. Further, from a simple conditioning viewpoint, patients should learn to avoid stimuli that occur regularly before anxiety onset, but this is not usual. Patients often avoid situations in which they would feel helpless if panic or the phobic stimulus occurred, even if they never experienced panic there, eg, tunnels or bridges. Situations, such as high grass, where snakes or insects might surprisingly appear, are shunned by these specific phobics, even if this experience has never occurred.

Unmodified learning theory is insufficient as a theory of anxiety, since it does not explain how phobias start, ie, the nature of the US, does not account for the limited variety of phobic stimuli, and gives the wrong predictors for the spread of avoidances. It is consonant only with the therapeutic efficacy of certain deconditioning procedures, but useless in explaining the equivalent effectiveness of alternative procedures that appear to work against deconditioning.

The equation of such animal behaviors with human neurosis raised many hackles regarding anthropomorphism and oversimplification. However, animal models are used in a thriving industry to (occasionally) discover humanly useful antianxiety agents. Many different procedures have been developed that nominally induce anxious anticipation and behavioral defenses against differing dangers. Remarkably, the intercorrelation of the effects of differing procedures is usually almost zero. This questions the presumption that "anxiety" univocally refers to a single adaptive function.

If neurosis is learned, why is it not spontaneously unlearned or extinguished? CRs extinguish when CSs fail to predict USs. This became known as the "neurotic paradox" and received many explanations. Paradoxically, behavioral learning theory, which eschewed mentalistic causal variables, in its current "modern" explanatory mode embraces predispositions such as anxiety sensitivity or catastrophizing tendencies. The historical controversy, typified by Hull and Tolman, is swept away by the ecumenical term "cognitive-behavioral." Further, contextual and enteroceptive CSs are freely invoked as modern "explanations" of anxiety disorders without demonstration of their existence, causal relevance, or predictive validation.

The other branch of conditioning theory, operant learning theory, appears relevant to specific phobic avoidances. If a signal regularly precedes an electric shock delivered through a particular patch of floor grid, then after thrashing about a dog could learn, that if, when signaled, they left that patch they would not be shocked. This avoidance response would not extinguish even if the electricity were turned off since the avoiding animal could not learn that the CS no longer signified real danger.

However, was this a model for chronic anxiety? Manifest emotionality ceased after the avoidance response was learned. However, if the dog was confined to the patch after the CS, emotional escape efforts occurred. These eventually ceased given repeated experiences that the CS no longer predicted shock. This supposedly laid the theoretical groundwork for effective exposure therapy for simple phobia, although it was already conventional grandmotherly wisdom that if one fell, then immediately getting back on the docile horse prevented the development of anxiety and riding avoidance.

Kraepelin

In a more directly relevant clinical tradition, Kraepelin closely, longitudinally, observed patients. Although Kraepelin[1] was primarily concerned with psychotic inpatients, he described spontaneous panic attacks accompanied by fears of dying in his lecture *Irrepressible ideas and irresistible fears* about a patient who developed severe agoraphobia and somatic preoccupation. He advocated exposure therapy, however, with pessimistic

expectations and cautioned against lengthy hospitalizations.

Kraepelin[2] also described both circumscribed and generalized social phobia noting that patients experienced "overpowering feelings of aversion […] when they had to establish relations of any kind with other patients," whereas other individuals, who appeared otherwise healthy, were "unable to urinate or write a letter in the presence of other people."

In the 6th edition of his textbook, he classified aspects of most contemporary anxiety disorders describing generalized anxiety (pervasive apprehensiveness and worry), obsessions (intrusive fears of contamination), compulsions (hoarding), the link between anxiety provoking obsessions and anxiety-reducing compulsive behaviors, phobias (fears of insects), agoraphobia, specific social phobia, and generalized social phobia.

These references to anxiety states have been generally ignored since his excellent syndromal descriptions and prognoses were denounced as fatalistic, and thoroughly obscured (at least in the United States) by the rise of psychoanalysis in the late 1940s. Superficial descriptive diagnosis was to be replaced by therapeutically relevant dynamic understanding of unconscious depths.

Freud

Freud's initial theory of anxiety was that accumulating libido, undischarged because of an unsatisfactory sexual life, as with abstinence or coitus interruptus, sufficed to cause an "actual" neurosis. Therefore, simple changes in sexual practices could cure anxiety. Freud's original descriptions emphasized anxiety attacks.

Freud then theorized that, in psychoneurosis, libido and aggressive drives were chronically undischarged because of persistent repression. The implicit assumption was that chronic anxiety, due to chronic repression, was the expectable symptom. Attacks were the occasional quantitative extreme with no particular significance. Simply advising patients about appropriate sexual hygiene was ineffective because it did not deal with the repressing forces.

Freud finally postulated a schema functionally identical with learning theory. Rising instinctual impulses, if ungratified, flood the infant with traumatic excitation equivalent to a US. The infant learns that certain situations, eg, the mother's absence, regularly precede a painful lack of gratification. Therefore, the mother's absence becomes a CS that releases anxiety, thus explaining separation anxiety.

Signal anxiety develops in situations regularly associated with forthcoming traumatic excitation, thus exactly paralleling conditioned anxiety. In learning theory, the conditioned drive of anxiety leads to escape behavior. This also has a parallel in Freudian theory, but the escape from internal excitation is into defense mechanisms.

Rising libidinal and/or aggressive impulses press for discharge, ie, action, but are met with threats of parental punishment (eg, castration), which are especially effective due to the race's past history. The threat of punishment leads to "objective anxiety," which seems definitionally indistinguishable from fear.

The increasing drives, the regular antecedents of punishment threats, become enteroceptive CSs that release signal anxiety. Escape results when signal anxiety mobilizes the overwhelming power of the pleasure principle that enforces drive repression, produces a fall in anxiety, thereby reinforcing repression. From repression causing anxiety, Freud moved to anxiety causing repression.

This theory received wide acceptance on the basis of supposed clinical benefits, although data supporting the existence of either benefits or repressive mechanisms was slim. However, relieving sexual repression seemed a good idea to many, which facilitated Freud's blanket acceptance by them, but incited demonization by contrary ideologies.

Imipramine: panics and agoraphobia

While working in a long-term psychoanalytic hospital, my initial interest in panic attacks came in 1959 with the serendipitous observation that imipramine blocked spontaneous panics (manifested by desperate appeals for help) in patients in whom long-term intensive psychoanalytic psychotherapy had failed. Chlorpromazine (considered then our most potent anxiolytic) actually exacerbated their symptoms. Controlled studies supported this observation. These patients would now be diagnosed as having panic disorder (PD) with agoraphobia.

Our model for the development of agoraphobia with panic attacks suggested that the initiating clinical event is the sudden appearance of spontaneous panics, abrupt crescendos of intense distress, and fearful apprehensions. Spontaneous means that there is no environmental danger sufficient to cause sudden extreme fear. Further, at illness onset, there are no specific phobic stimuli.

The spontaneous panic immediately leads to an outburst of appeals and attempts to get help, eg, telephone calls, precipitous emergency room visits, etc. After the initial attack, the patient may temporarily feel well, but after recurrent panics, enduring apprehension, chronic tension, and autonomic distress develop. The chronic distress fluctuates, but lacks the dramatic panic crescendo. Interpanic chronic anxiety probably has several components. Concern about panic recurrences causes chronic anticipatory anxiety, which is explicable by the uncertainty, insecurity, and helplessness engendered by unpredictable attacks. However, patients also report good days and bad days. On awakening, they may correctly realize that this will be a bad day in which panics are likely to occur. Conversely, they may feel fairly well and unlikely to panic, although not immune. This waxing and waning of interpanic anxiety cannot be entirely explained on the basis of learned, anticipatory fears.

During imipramine treatment, there is a regular progression of antipanic effects. After several weeks, patients no longer have spontaneous full-blown panics. However, they often feel as if a panic is starting and helplessly observe their increasing distress, which suddenly, surprisingly, stops and does not peak into terror. (This experience is inconsistent with the theory that panic is simply a catastrophic overreaction to autonomic fluctuations.) Many recollect having such limited symptom attacks such as these between panics when not on medication. In Freud's early lucid description of the agoraphobic process, he refers to "larval" anxiety attacks, which probably contribute to interpanic chronic anxiety. A third component of interpanic chronic anxiety may be sensitization, which occurs following repeated unexpected traumas, ie, panics. The sensitized organism overreacts to both conditioned and neutral stimuli, resulting in maintained tension. (In *Aplysia*, sensitization is due to presynaptic facilitation of neurotransmitter release by sensory neurons and structural changes that facilitate this functional increment.)

Some equate the interpanic anxiety with the anxiety of generalized anxiety disorder (GAD). Further, since imipramine benefits GAD, this is held by some to obviate the distinction between anxiety and panic in PD. This notion is incorrect on several counts. In PD, imipramine benefits acute somatic distress, particularly dyspnea, whereas low-potency benzodiazepines ameliorate anticipatory anxiety. In GAD, the reverse is true. Imipramine and selective serotonin reuptake inhibitors (SSRIs) benefit worrisomeness, whereas benzodiazepines relieve somatic distress, ie, muscular tension rather than autonomic distress.

Further, within PD, imipramine benefits panic associated with acute dyspnea (which is not a feature of acute danger–incited fear or GAD) more than alprazolam. Conversely, alprazolam is superior to imipramine in panics limited to palpitations, sweating, and tremor—the cardinal features of danger-incited fear. This issue is an example of confusing useful pharmacological dissection with superficially observed pharmacological amalgamation.

Once chronic interpanic anxiety develops, the patient often comes to believe that certain situations elicit panic, although, inexplicably, sometimes they do not. Patients also conclude that they are more prone to panic when alone or away from home. Therefore, they constrict traveling and demand companionship, believing that this decreases panic likelihood. They primarily avoid situations where they could not easily get help if panic strikes. Illness course is quite variable. Some develop panic attacks, but do not go on to marked chronic interpanic anxiety. This course would be unexpected if conditioning sufficed for chronic interpanic anxiety. Some slowly develop an increasing range of avoidances, whereas others precipitously plunge into a housebound state. The initial phase is dominated by apprehension of recurrent unpredictable panics. However, by the time the patient receives psychiatric attention, they focus on their constricted life, multiple avoidances, chronic anxiety, and high level of friction with family members drafted as guardians. Patients often believe that panics decrease in frequency, attributing this to phobic avoidances. This "post hoc" attribution is only partly true since exposure therapy does not cause any substantial increase in panics, although it may exacerbate anticipatory anxiety. It is not clear if spontaneous panics usually decrease in frequency over time, although this is frequently reported.

Imipramine's primary pharmacological effects are directly antipanic, requiring less than 6 weeks to take maximum effect, given adequate dosage. The spontaneous panic is blocked, first in its stark manifestation as a groundless crescendo of terror, and then in its larval form. We do not believe that there is any immediate pharmacological effect of imipramine upon either anticipatory anxiety or avoidant behavior. However, the antipanic effect allows patients to continue to expose themselves to avoided situations without set-back by

occasional panic. This provides the setting for increasing, indirect, nonpharmacological benefits on anticipatory anxiety and avoidance. On exposure, some become nonphobic despite continued panics, as if they become stoically convinced that panics are transient and more upsetting than dangerous.

Challenges

When it was discovered that lactate infusions, under controlled, double-blind circumstances, regularly precipitated panic in patients prone to panic, but not in normal subjects, an instant argument started. Was the lactate doing anything biochemically or physiologically specific or was it simply a stress reminding only the patients of past panics, therefore throwing only them into a panic? In rebuttal, Pitts demonstrated that infusion of EDTA, a powerful calcium-chelating substance, actually threw patients into tetany, but nonetheless did not produce panic. This lactate specificity has been amply documented because such noxious agents as physostigmine, insulin, 5-hydroxytryptamine, etc, also fail to precipitate panic attacks. Nonetheless, the conviction that the spontaneous panic attack was misplaced fear persisted, protecting the basis of several psychogenic theories.

The discovery that antidepressants that blocked the clinical panic attack also blocked lactate-induced (and later CO_2-induced) panic attacks made it seem likely that these laboratory-induced panics closely modeled the real clinical experience. This was supported by the inefficacy of lactate in producing panics in other anxiety disorders.[3] Also, counterintuitively, lactate-induced panic, and later CO_2-induced panic, did not result in fear-like stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. Adenocorticotropic hormone (ACTH), cortisol, and catecholamines, as well as 3-methoxy-4-hydroxyphenylglycol (MHPG), stayed flat or decreased during the attack. Further, cannulating ambulatory patients demonstrated that spontaneous clinical panic did not cause cortisol increases.

Another peculiar aspect of spontaneous clinical panic, especially those that led to marked anticipatory anxiety and eventually to agoraphobia, was the salience of dyspnea (air hunger) as an attack symptom. This was usually attributed to hyperventilation because patients often seem to hyperventilate during panic. In fact, many attributed panic attacks to acute hyperventilation and respiratory alkalosis. However, to our surprise, we found that directed voluntary hyperventilation did not regularly cause panic attacks in either patients or normal subjects, nor did it cause air hunger nor did it relate to respiratory alkalosis. Furthermore, studies indicate that palpitations, sweating, and trembling are features of fear during mortal danger, but dyspnea is not.

Suffocation false alarm theory

Increases in brain lactate and plasma CO_2 indicate impending suffocation. Combined with panic-induced hyperventilation and acute dyspnea, this suggested that the spontaneous panic attack may be a suffocation false alarm. That is, there is an evolved specific suffocation alarm system that, when pathologically disturbed, is triggered by minor physiological signals of impending suffocation, such as a rising blood CO_2 level or an increasing brain lactate level.

This is supported by much consonant evidence.[3] Briggs et al[4] used factor and cluster analysis to distinguish patients with dyspneic panic attacks, who responded better to imipramine than alprazolam. The patients with nondyspneic panic attacks responded better to alprazolam than imipramine.

A major incongruity with "panic equals fear" theorizing is the transience of the attack. Fear does not stop until the danger has gone. The spontaneous panic attack usually terminates after 4 minutes of marked distress. Perhaps this is due to acute hyperventilation adaptively dropping the blood CO_2 level while raising oxygenation, thus assuring the suffocation monitor that suffocation is not impending, which terminates the alarm. This is in keeping with the frequent finding of chronic hyperventilation and hypocapnia due to frequent sighing in panic patients.

That the HPA system is inhibited during panic may be because HPA release causes a precipitous rise in metabolic oxidation, which would be counterproductive under asphyxiating circumstances.

Further, Perna et al[5] found that subjects with a history of unexpected panic attacks had a high rate of family history of PD, and that first-degree asymptomatic relatives of PD patients had a much higher rate of CO_2 sensitivity than normal subjects.[6] Further, Perna et al[7] showed that the PD probands with CO_2 hypersensitivity accounted for most of the familial loading. CO_2 hypersensitivity may be due to a particular genetic dysfunction among the multiple phenotypes called PD. It may cut across current syndromal boundaries.

The relevance of respiratory CO_2 sensitivity to the genetics of PD receives remarkable confirmation by Bellodi et al[8], who amplify the classic diagnostic concordance study of identical and fraternal twins by administering CO_2 challenges. With regard to PD, probandwise concordance rates were higher for monozygotic pairs (6 out of 9, 67%) than for dizygotic pairs (neither out of 2, 0%). For spontaneous panic attacks, the respective rates were 71% and 18%. For CO_2-induced panic attacks, the respective rates were 56% and 13%. These marked differences, if replicated in larger samples, indicate that the genetic relationship is not simply additive, but may be the emergent outcome of genetic interactions. Such complex genetics make attempts to link disease to single DNA regions even more problematic.

The search for cerebral markers is of great interest, but, lacking a detailed theory of how psychopathology relates to cerebral dysfunction, we must recognize that this is useful and exploratory, rather than definitive, work. Unfortunately, the history of biological psychiatry is replete with reports of baseline differences between patients and normal subjects that turn out to be artifacts, since these are not randomized, experimental studies, but naturalistic, multiply confounded studies. The differences between patients and normal comparison subjects that have stood up best have been due to challenge studies, eg, lactate infusion, sedation threshold, CO_2 inhalation. Many psychopathologies may be due to adaptive deficiencies in cybernetic control mechanisms, best revealed by perturbing the system rather than simply observing it at rest. Combining challenges with genetic studies may prove a useful strategy in dealing with the multiple phenocopy problem.

Congenital central hypoventilation syndrome

The discovery that children with congenital central hypoventilation syndrome (CCHS), who die from sleep apnea unless artificially ventilated, lack respiratory or affective response to CO_2 inhalation, makes it clear that the suffocation alarm system actually exists.

I speculate that the benefits of serotonergic antidepressants are due to downregulation of this hypersensitive system. That children with CCHS, who have hardly any suffocation alarm system at all, should have their breathing inhibited by imipramine counterintuitively verifies that theory. Further, that these mortally endangered children, protected by anxious parents and fallible technology, should not be anxious, directly contradicts modeling and conditioning theories of anxiety. CCHS is rather like PD inside out.

Other findings support this theory, in particular, the frequency of PD in respiratory disease. Other findings suggest heterogeneity of the panic syndrome. In particular, the relationship to gastrointestinal disease, vestibular disorder, and premenstrual syndrome indicates that substantial extensions are in order.

The marked parallelism between Freudian and learning theory is due to their common emphasis on contiguity conditioning, which leads to anxiety as a signal of anticipated traumatic states. Neither theory distinguishes between panic attacks and chronic anticipatory anxiety, therefore, neither is consonant with the specific benefit of antidepressants on PDs.

Separation anxiety

Patients with agoraphobia often show clinging, dependent behavior and intolerance of being alone. The histories of severely impaired agoraphobic inpatients indicated that 50% recalled distinct separation anxiety disorder. Moreover, initial panic episodes were often preceded by significant personal losses, which perhaps indicated that some special early predilection for separation anxiety might be later manifested as agoraphobia.

The initial Freudian theory of separation was not much help because it was simply another form of contiguity conditioning. Separation anxiety required recognition of the mother as a distinct object, the discrimination of her presence versus her absence, and the association of states of mounting tension with her absence. Freudian theory offered no basis for postulating a distinctive drug effect on separation anxiety any more than on any other anxiety.

Freud's description of object choice could also be phrased in conditioning parlance. The US was oral gratification; the UR was pleasurable drive reduction. The CS was mother's presence preceding the oral gratification (UR). Eventually, the mother (CS) released hopeful contentment (CR): the conditionable component of tension decrease. Therefore, the infant attached to the mother as a need gratifier.

It struck me that perhaps early separation anxiety was not like anticipatory anxiety, but due to an evolutionarily distinct process. Similarly, a learning theory of attachment via reinforcement seemed dubious. Bowlby also

argued that the child's tie to the mother did not depend on learning that she was a need gratifier but antedated such learning, thus resembling the ethological notion of imprinting. Furthermore, separation anxiety did not depend on learning that the mother's absence was associated with distress, but was an evolved innate protest mechanism, instinctively released by separation during the appropriate helpless developmental phase.

Distress after separation from nest or mother occurs in infant animals who could not yet have learned that separation means failure to gain relief from instinctual tension. The early lost piping of chicks separated from their nests and whining of puppies separated from the mother are clear examples. Separation anxiety occurs when infant monkeys raised in peer groups are separated from each other, although mothering does not exist in such groups. Harlow's experimental work demonstrated that the developmentally isolated monkey attached to the contact comfort of a terry cloth model rather than to a wire feeder. Oral gratification was not the basis for object attachment. Naturalistic observation could never have produced this trenchant conclusion.

Separation anxiety, to the degree that it is learned, builds on an innate adaptive mechanism that causes an alarm, intense psychic distress, under conditions of naive separation. The evolutionary "purpose" is to cause the vulnerable infant to emit anguished signals that elicit maternal retrieval. Obviously, the helplessly dependent lost infant is fair game for predators. Even in the absence of predators, if the mother cannot find the infant, a dehydrated, weakened infant results. If hunger pain was necessary before emitting distress cries, many infants would die or be impaired. Evolutionarily, a built-in (unlearned) early warning alarm system for maternal recall makes good sense. It is better to cry before being actually hurt. Any biological control mechanism has a wide range of variations in strength and threshold. Perhaps some children have constitutional, familial, or pathogenic vulnerabilities. If antidepressants specifically raise this alarm threshold, panic is prevented, but no immediate effect on anticipatory anxiety should occur. It is striking that the only drugs that have this specific antipanic action are certain antidepressants (and morphine). High-potency benzodiazepines affect both processes.

In a detailed longitudinal study of over 1000 children between ages 3 and 18, Poulton et al[9] found self-reported separation anxiety largely, but not entirely, independent of experience. Before age 11, separation anxiety was only independently correlated with mothers' "fear of going out alone," which can be interpreted from either modeling or genetic viewpoints. However, the amount of variance accounted for was only 2.5%.

Initially, I speculated that all antidepressants would ameliorate both separation anxiety and spontaneous panic. This generalization was faulty, since we already knew that electroconvulsive therapy (ECT) did not ameliorate panic. Later work with bupropion and maprotiline demonstrated that some pharmacological antidepressants failed as antipanic agents. However, the benefit of imipramine did generalize to the other tricyclic antidepressants, as well as the SSRIs and monoamine oxidase inhibitors (MAOIs).

Theories of separation anxiety had important effects on treatment. Anna Freud considered school phobia a true psychoneurosis caused by repressed hostility toward the mother, rather than an upwelling of separation anxiety. The child magically believes unconscious hostility takes effect. To reassure him- or herself that this is untrue, the child insists on mother's presence. Therefore, the proper treatment is play analysis to express and relieve unconscious hostility, without concern for return to school, since school refusal is only a symptom.

Eisenberg observed that such children often never get back to school. He reconceptualized school phobia as resulting from maternal anxiety over the child's individuation. This was communicated to the child making him secondarily anxious. Therefore, proper treatment was putting the mother into psychotherapy and insisting on the child's immediate return to school. The psychotherapist made sure that the mother did not sabotage this return.

This proved effective in approximately 75%. However, the other 25% proved refractory. We demonstrated, in a pilot study and then in a double-blind, placebo-controlled study, that children with such refractory school phobia responded to imipramine.

Endogenous opioids

The important works of Panksepp, Suomi, and Kalin shows that separation anxiety is controlled by an endogenous opioid system. It can be specifically ameliorated by morphine (and imipramine) and exacerbated by naloxone, the opioid receptor blocker.

It seemed too great a coincidence that endogenous opioids controlled both separation anxiety and respiratory

driving by CO_2. That an endogenous opioidergic dysfunction may underlie both the proneness to separation anxiety and to suffocation false alarms was proposed. This received recent preliminary experimental support from pilot work showing that normal subjects, usually unresponsive to intravenous lactate, develop acute dyspnea, distress, and hyperventilation when intravenous lactate is preceded by naloxone.

Conclusion

This incomplete, highly personal, historical note provokes the following generalization: our folk terms for emotional distress are far too broad. Over evolutionary time, organisms were faced by many recurrent natural and social dangers. Natural selection fostered the development of a complicated webwork of monitors, alarm reactions, and specific physiological facilitators of many distinct behavioral adaptations. We have not discussed social anxiety disorder, which may have childhood behavioral inhibition as an antecedent. Peculiarly, it responds to MAOIs, but not to tricyclic antidepressants, indicating a distinct physiological regulation and impairment. The development of an alarm system, keyed to social disapproval, would seem advantageous to a highly social species. Judith Rapoport has suggested that cleaning compulsions may be incited by a hypersensitive release of grooming and self-cleaning monitors.

All-purpose learning mechanisms are primarily attuned to nonemergency situations, where both repetitive drill and cognitive insights enhance skills that have not been evolutionarily honed. Appetitive, flexible, goal-seeking, nonemergency activities are the best context for such learning. States of maladaptive, chronic distress are not learned, but reflect malfunctioning alarms. Learning can develop compensatory devices, eg, stoicism to mitigate malfunctions, in a goal-seeking context.

Recent studies indicating the responsiveness of panic attacks (in largely nonagoraphobic patients) to cognitive-behavioral therapy (CBT) are of interest, but do not validate conditioning theory. If anything, their results contradict it, since antipanic effects occur far too rapidly for either enteroceptive deconditioning or decatastrophizing of chronic attitudes to occur, nor has this therapeutic sequence been demonstrated. Adequate comparative trials with non-CBT therapies have had inconsistent differential benefits. Follow-up indicates a waxing and waning of symptomatology, which does not follow from CBT theory. Perhaps a therapeutic response of separation anxiety to a strong persuasive ally provides an alternative explanation for antipanic benefit. This has not been investigated.

Only collaboratively conducted, expert, controlled experimental approaches will enable the identification of covert adaptive systems and their dysfunctions. Objective measurements and analyses by collaborators with differing views are required to obviate self-serving reports dominated by allegiance effects. ❑

REFERENCES

1. Kraepelin A. *Lectures on Clinical Psychiatry*. 1904. Johnstone T, ed. New York, NY: Hafner Pub Co; 1968.
2. Kraepelin E. *Clinical Psychiatry*. Metoui H, trans; Quen JM, ed. Canton, Mass: Science History; 1899.
3. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry*. 1993;50:306-317.
4. Briggs AC, Stretch DD, Brandon S. Subtyping of panic disorder by symptom profile. *Br J Psychiatry*. 1993;163:201-209.
5. Perna G, Gabriele A, Caldirola D, Bellodi L. Hypersensitivity to inhalation of carbon dioxide and panic attacks. *Psychiatry Res*. 1995;57:267-273.
6. Perna G, Cocchi S, Bertani A, Arancio C, Bellodi L. Sensitivity to 35% CO_2 in healthy first-degree relatives of patients with panic disorder. *Am J Psychiatry*. 1995;152:623-625.
7. Perna G, Bertani A, Caldirola D, Bellodi L. Family history of panic disorder and hypersensitivity to CO_2 in patients with panic disorder. *Am J Psychiatry*. 1996;153:1060-1064.
8. Bellodi L, Perna G, Caldirola D, Arancio C, Bertani A, Di Bella D. CO_2-induced panic attacks: a twin study. *Am J Psychiatry*. 1998;155:1184-1188.
9. Poulton R, Milne BJ, Craske MG, et al. A longitudinal study of the etiology of separation anxiety. *Behav Res Ther*. 2001;39:1395-1410.

Aspectos históricos de la ansiedad

"Ansiedad" es un término clave para observaciones y teorías conductuales, psicoanalíticas, neuroendocrinas y psicofarmacológicas. Resulta difícil hacer una revision relacionado con los aspectos históricos, ya que la historia es basicamente un estudio de los datos originales. Desafortunadamente numerosas anécdotas clínicas noe corresponden con registros los objetivos iniciclos. Incluso reportes de estudios objetivos pueden sufrir los efectos de la lealtad. Por lo tanto este ensayo refleja primariamente el impacto personal del trabajo de otros comparado con el trasfondo de mi experiencia clínica y científica. Todo esta lleva a poner en duda de que la "ansiedad", tal como existe en los trastornos sindromáticos, sea simplemente el extremo cuantitativo de la "ansiedad" normal que ocurre durante la anticipación del peligro. Se presenta una visión alternativa que enfatiza alteraciones de diferentes sistemas de alarma adaptativos y evolucionados.

Aspects historiques de l'anxiété

L'«anxiété» est un terme-clé pour les théories et les observations comportementales, psychoanalytiques, neuroendocrines et psychopharmacologiques. Faire un commentaire sur son aspect historique est difficile, puisque l'histoire se fonde, à proprement parler, sur l'étude des données premières. Malheureusement, beaucoup d'anecdotes cliniques ne correspondent pas au rapport des faits survenus il y a longtemps. Même les comptes rendus d'études objectives peuvent souffrir d'effets d'allégeance. Le présent article est donc principalement le reflet de l'impact personnel du travail d'autres sur toile de fond de mes expériences cliniques et scientifiques. Cela me conduit à m'interroger sur l'hypothèse selon laquelle l'«anxiété», telle qu'elle existe dans les troubles syndromiques, est simplement l'extrême manifestation quantitative de l'«anxiété» normale qui apparaît lors de l'anticipation face au danger. Une autre thèse est présentée, qui souligne les dysfonctionnements de systèmes d'alarme adaptatifs ayant évolué de façon spécifique.

Nonpharmacological treatments for anxiety disorders

Jean Cottraux, MD, PhD

An evidence-based review of nonpharmacological treatments for anxiety disorders is presented. The vast majority of the controlled research is devoted to cognitive behavior therapy (CBT) and shows its efficiency and effectiveness in all the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) anxiety disorders in meta-analyses. Relaxation, psychoanalytic therapies, Rogerian nondirective therapy, hypnotherapy, and supportive therapy were examined in a few controlled studies, which preclude any definite conclusion about their effectiveness in specific phobias, agoraphobia, panic disorder, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD). CBT was clearly better than psychoanalytic therapy in generalized anxiety disorder (GAD) and performance anxiety. Psychological debriefing for PTSD appeared detrimental to the patients in one high-quality meta-analysis. Uncontrolled studies of psychosurgery techniques for intractable OCD demonstrated a limited success and detrimental side effects. The same was true for sympathectomy in ereutophobia. Transcranial neurostimulation for OCD is under preliminary study. The theoretical and practical problems of CBT dissemination are discussed.

Dialogues Clin Neurosci. 2002;4:305-319.

Keywords: *anxiety disorder; meta-analysis; controlled trial; cognitive-behavior therapy; psychological therapy; debriefing; psychosurgery*

Nonpharmacological treatments for anxiety disorders—although of varied orientations—are unequally represented in the literature. The bulk of the research is devoted to behavior therapy (BT) and, more recently, to cognitive therapy (CT) methods. Both CT and BT techniques are used in combination by the vast majority of clinicians and researchers under the label of cognitive behavior therapy (CBT). Relaxation methods have been used as the main technique in anxiety disorders or studied as a control condition in some randomized controlled trials (RCTs). Some relaxation techniques, such as Ost's applied relaxation,[1-3] are in fact made of several cognitive and behavioral techniques. Psychoanalytic (or psychodynamic) therapies, hypnotherapy, Rogerian nondirective therapy, supportive therapy (ST), and psychological debriefing for posttraumatic stress disorder (PTSD) have been evaluated in RCTs and meta-analyses. Transcranial neurostimulation and psychosurgery techniques have been studied in obsessive-compulsive disorders (OCDs). Some preliminary data exist for sympathectomy in ereutophobia. Hence an evidence-based review of all these nonpharmacological methods is possible.

Panic disorder and agoraphobia

CBT in panic disorder and agoraphobia

Panic disorder and agoraphobia are treated using two basic strategies: exposure (in imagination and in vivo or interoceptive exposure) and cognitive restructuring.

Author affiliations: Jean Cottraux, MD, PhD, Anxiety Disorder Unit, Hôpital Neurologique, Lyon, France

Address for correspondence: Jean Cottraux, MD, PhD, Anxiety Disorder Unit, Hôpital Neurologique, 59 boulevard Pinel, 69394, Lyon, France (e-mail: cottraux@univ-lyon1.fr)

Selected abbreviations and acronyms

BDZ	*benzodiazepine*
BT	*behavior therapy*
CBT	*cognitive behavior therapy*
CT	*cognitive therapy*
EMDR	*eye movement desensitization and reprocessing*
GAD	*generalized anxiety disorder*
OCD	*obsessive-compulsive disorder*
PTSD	*posttraumatic stress disorder*
RCT	*randomized controlled trial*
SSRI	*selective serotonin reuptake inhibitor*
SST	*social skills training*
ST	*supportive therapy*

Exposure principle

Exposure in vivo represents the final common pathway of many techniques described by several schools of psychotherapy. The first person to write a report on successful exposure in agoraphobia was a French author, Perroud[4] who was working at the Hôpital de la Charité, in Lyon. Janet[5] used the exposure principle in several cases of obsessions or phobias. Later, Freud[6] made a forgotten contribution to CBT with the straightforward judgement that for resistant agoraphobia "one succeeds only when one can induce them by the influence of the analysis to go into the street and to struggle with their anxiety." In this respect, cognitive behavior therapists are more Freudian than modern psychoanalysts, who continue to treat agoraphobia with classic psychoanalysis, while its effectiveness remains to be demonstrated.

Wolpe[7] and Marks,[8] a fervent reader of Janet, systematically developed the exposure paradigm in anxiety disorders and put this principle under systematic scientific inquiry, in several controlled trials, which were replicated all over the world.

Exposure consists in habituating degree by degree the patient to the feared situations in imagination and then in vivo. The aim is to obtain a habituation of emotional responses and the extinction of avoidance behaviors, which are reinforced by anxiety. Generally, the therapy starts with exposure in imagination confronting the patient step by step to the feared situations until habituation occurs. Graded in vivo exposure is then carried out. Each session of exposure in vivo or in imagination may last up to 45 minutes, which is, in general, the maximum length of time required to habituate the anxiety responses.

Cognitive restructuring

CT implements two main strategies: (i) cognitive restructuring on misinterpretations of bodily sensations; and (ii) breathing retraining in order to control the physiological effects of hyperventilation and tachycardia. Treatment typically includes 15 to 20 sessions, which can be summarized as follows:

- *Modifying panic attacks*. (i) Breathing retraining to control the sensations resulting from hyperventilation frequently involved in panic attacks; (ii) Valsalva technique through abdominal breathing to control tachycardia; and (iii) cognitive restructuring to modify misinterpretations of bodily sensations and challenge the danger cognitive schemata.
- *Modifying agoraphobia*. Behavioral experiments consist in modifying avoidance behaviors through graded exposure followed by cognitive restructuring through self-talk and written disputing on appropriate forms.

Interoceptive exposure for panic attacks

Some researchers designed specific techniques for the bodily symptoms. Panic control treatment[9] consists of three major strategies: (i) cognitive restructuring; (ii) breathing retraining; and (iii) interoceptive or structured exposure to bodily sensations that have become associated with panic attacks.

Since physical sensations often trigger conditioned anxiety, the procedure of interoceptive exposure attempts to extinguish anxiety connected with these bodily sensations. Identifying "interoceptive avoidance," or avoidance of situations that might provoke specific physical sensations and their catastrophic cognitive appraisal, is implemented during the therapy. These situations are not identical to agoraphobic situations and may include watching frightening movies or driving with the windows closed. All patients are presented with exercises meant to induce physical sensations: running on the spot, being spun in a swivel chair, breathing through a narrow straw, etc. Patients are then encouraged to enter naturalistic situations that might be associated with the elicitation of physical sensations that are particularly anxiety-provoking.

Outcomes of exposure treatments

Meta-analyses on panic disorder[10-13] found that in vivo exposure was a critical component of treatment, but disagreed on its results in combination with antidepressants, anxiolytic drugs, and cognitive interventions. Van Balkom et al's[13] meta-analysis and its follow-up study by Bakker et al[14] suggested that the most effective treatment was a combination of exposure in vivo and antidepressants. Another meta-analysis by Gould et al[15] found a higher size effect for CBT than for pharmacotherapy and a combination of medication with therapy, with the lowest dropout rate and the best cost–effectiveness ratio. *Table I* presents the outcomes of Gould et al's[15] meta analysis. Interoceptive exposure appears to be the most effective technique.

Outcomes at follow-up

O'Sullivan and Marks[16] conducted a review of 10 long-term follow-ups (the longest lasted 9 years). Four hundred and forty-seven patients out of a panel of 553 had been followed up in controlled studies for a mean duration of 4 years. They found a 76% improvement in the cumulated samples with residual symptoms as a rule; 15% to 25% of the patients continued to have depressive episodes after treatment. In the longer follow-ups, up to 50% consulted practitioners for their psychological problems and 25% saw psychiatrists for depression and/or agoraphobia. However, the consultation rate decreased.

CBT and medication: combination studies

Combination allows stopping the medication without the very high relapse rate that is found in drug-only studies. However, a positive interaction was found only with certain antidepressant drugs (imipramine, fluvoxamine, and paroxetine) and anxiolytic drugs (buspirone). Moreover, CBT facilitates the withdrawal of benzodiazepines (BDZs). One may summarize the outcomes of the combination studies as follows:

- Positive interactions with antidepressants were reported in seven controlled studies.[17-23]
- No interaction with antidepressants was found in five studies.[24-28]
- Short-term positive interaction and long-term *negative* interaction of exposure in vivo with high doses of alprazolam (6 mg) was found by Marks et al[29] and Wardle et al.[30]
- Short-term positive interaction of exposure in vivo with low doses of diazepam (<30 mg) was found in a controlled study. However, there was a transient withdrawal syndrome. No negative long-term effects.[31]
- Short-term positive interaction of CBT with low doses of buspirone (<30 mg) on agoraphobia and generalized anxiety was demonstrated in a controlled study. No withdrawal syndrome and no long-term negative effects appeared. The effect of buspirone on agoraphobia correlated with its effects on depressive cognition. Buspirone's action on agoraphobic behaviors is probably mediated by the reduction of both anxiety and depression.[32]
- CBT facilitated BDZ withdrawal in two controlled studies.[33,34]

Therapy	Size effect
CT + interoceptive exposure	0.88
CBT	0.68
Pharmacological treatment	0.47
Pharmacological treatment + CBT	0.56
Antidepressants	0.55
Benzodiazepines	0.40

Table I. Panic disorder: meta-analysis of size effects.[15] CT, cognitive therapy; CBT, cognitive behavior therapy.

Relaxation in panic disorder and agoraphobia

CT appeared to be superior to Jacobson's relaxation in one trial.[35] In a 2-year follow-up study, Craske et al[35] suggested that Jacobson's relaxation could even impede the positive effects of BT.

Clark et al[36] found that CBT (84%) was superior to relaxation (40%), imipramine with a maximum dose of 300 mg/day (42%), and a waiting list. The follow-up of this study was 1 year. At this point, all intention-to-treat groups received self-exposure instructions. This study confirmed the superiority of CBT over relaxation and also suggested that imipramine, the reference drug, was neither the only effective treatment nor the most efficient.

Applied relaxation[1-3] has been found to be as effective as CBT in panic disorder with agoraphobia. However, it contains cognitive coping strategies, as well as exposure assignments. Accordingly, the applied relaxation format is more a variant of CBT than a pure relaxation tech-

nique. This is confirmed by the fact that applied relaxation appeared better than Jacobson's relaxation in one controlled trial.[37] Nevertheless, applied relaxation was superior to a waiting list, but inferior to CT in another trial dealing with panic disorder *without* agoraphobia.[38]

ST in panic disorder

In a controlled study, Beck et al[39] reported a rate of 71% panic-free patients after 8 weeks of CT versus 25% after 8 weeks of ST. It is worth noting that 94% of the patients who were randomized to ST chose to have CT after ST. At a 1-year follow-up 87% of the patients who had CT were panic-free versus 79% in the group who had ST first and then CT. Beck et al's[39] outcomes were at variance with those of Shear et al's[40] controlled study, which found at a 6-month follow-up that CT and ST demonstrated positive and equivalent effects on panic attacks.

Psychodynamic therapy in panic disorder

To our knowledge, there is only one controlled study concerning panic disorder. Wiborg and Dahl[41] compared clomipramine alone with psychodynamic therapy (15 sessions) associated with clomipramine in 80 subjects with panic disorder. Psychodynamic therapy was focused on dependence behaviors and related emotional problems. The randomization process did not work in that study: baseline Hamilton Anxiety, Hamilton Depression, and Handicap scales were significantly higher in the clomipramine group. Nevertheless, the authors contended that the combined condition (20% relapses) was superior to clomipramine alone (75% relapses) at a 9-month follow-up. As there was no waiting-list control, Wiborg et al's[41] study does prove a specific effect of psychodynamic therapy in panic disorder.

Generalized anxiety disorder

CBT in GAD

Methods

Since the first operational definition of generalized anxiety disorder (GAD) in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (*DSM-III*),[42] the pathogenesis has been clearly concentrated on the concept of excessive worry.[43] This cognitive point of view considers the somatic symptoms as secondary manifestations of cognitive processes. Later, the *DSM-IV*[44] paid allegiance to the cognitive model with another criterion: the difficulty in controlling the worry. This new trend was supported by numerous studies assessing normal and abnormal thoughts showing the intolerance to uncertainty of GAD subjects. Pathological worry is viewed as shaped by cognitive distortions, which result from maladaptive schemata of danger. Ruminations and attention disturbances impede normal problem solving in everyday situations and worry represents for the patient an inefficient way to control possible negative events in the future.[45]

In CBT, the patient is advised to consider his or her catastrophic view up to its ultimate consequences. At this point, Socratic questioning will help him or her substitute more probabilistic views instead. The patient can also be exposed in imagination to the catastrophic scenes to reach habituation. Then, basic schemata of danger are elicited and questioned. The treatment format classically involves about 15 sessions. The different levels of intervention are cue-controlled relaxation, cognitive restructuring, problem solving, in vivo exposure to feared real-life situations, and exposure in imagination in order to obtain habituation to highly improbable situations. The aim is to replace the worry by effective coping strategies.

Outcomes

A meta-analysis by Gould et al[46,47] found CBT and pharmacotherapy equally effective. This meta-analysis included 35 controlled studies, which had been published between 1974 and 1996: 13 studies dealt with CBT and 22 with medication. The size effect was 0.70 for CBT and 0.60 for the pharmacological treatment. However, the drug samples had higher dropout rates and showed a loss of efficacy at withdrawal, while the effects of CBT were maintained. Studies assessing the CBT plus drug combination were lacking.

Psychoanalytic therapy in GAD

Two studies reported negative outcomes for psychoanalytic therapies *(Table II)*.[48-53] In Durham et al's[48] study psychoanalytic therapy had within-group positive effects, but these effects were significantly inferior to those of CBT immediately after the test and at 1-year follow-up.

One should also mention that the psychoanalytic method used by White[49] was less than optimal.

Rogerian nondirective therapy in GAD

Two studies reported equal effects of Rogerian therapy and CBT. Two reported a better effect of CBT. Further studies should be done to clarify this point. *Table II* also presents the outcomes of these four studies.[50-53]

Posttraumatic stress disorder

CBT in PTSD

Methods

Treatment of PTSD is the center of a growing interest in the literature. Therapeutic programs involve relaxation, which is beneficial in case of high emotional arousal, exposure to avoided situations or images related to the trauma, and CT. Five methods have been proposed. All the methods insist on the necessity of respecting the pace of the patient to reach the peak of the horror that is at the center of the traumatic experience.

- *Systematic desensitization* presents the feared stimuli in imagination under relaxation in a graded way prior to in vivo exposure.
- *Exposure in imagination and in vivo* aims at habituating the patient to the aversive stimulus, by reducing abnormal reactivity and avoidance. In vivo exposure to the nondangerous situations being avoided is then suggested.
- *Stress management* emphasizes the development of coping strategies to deal with fears (relaxation, social skills training [SST], modification of anxious verbalization, or thought stopping).
- *Cognitive therapy* also suggests exposure in imagination and representation of coping strategies, but puts a greater emphasis on dealing with automatic thoughts and dysfunctional attitudes (personalization, guilt, illusion of a safe world, and necessity of revenge).
- *Eye movement desensitization and reprocessing (EMDR)* consists in inducing eye movements when concentrated on feared imagery, bodily sensations, and negative statements associated with the trauma, in order to reduce anxiety and hence modify cognition in a positive way.[54] Sessions last 90 minutes and are limited to 4 or 5. This method was hypothesized to work on neuropsychological functions. In fact, there is no clear evidence that EMDR is no more than a variant of the usual CBT programs. A controlled study[55] found that EMDR with or without ocular movements gave the same positive outcomes as a standard psychiatric procedure at posttest and a 6-month follow-up. Nonspecific factors might be implied in EMDR.

Outcomes: meta-analysis

Most of the studies showed positive results. There is no difference in outcomes between CT and BT.[56] About 60% of patients respond to the treatment. Follow-up studies seldom exceed 6 months or 1 year.

Van Etten and Taylor[57] conducted a meta-analysis of 61 treatment outcome trials for PTSD. Treatments included drug therapies (tricyclic antidepressants, carbamazepine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors [SSRIs], and BDZs), psychological therapies (BT, EMDR, relaxation training, hypnotherapy, and psychodynamic therapy), and control conditions (pill placebo, waiting-list controls, supportive psychotherapies, and nonsaccade EMDR control). Psychological therapies demonstrated significantly lower dropout rates than

Outcome	Duration of follow-up	Reference
• *CBT versus psychoanalytic therapy*		
CBT > psychoanalytic therapy	1 year	Durham et al,[48] 1994
CBT > psychoanalytic therapy		White et al,[49] 1992
• *CBT versus Rogerian nondirective therapy*		
CBT > ST	6 months and 1 year	Borkovec and Mathews,[50] 1987
CBT > ST	1 year	Borkovec and Costello,[51] 1993
CBT = ST	6 months	Blowers et al,[52] 1987
CBT = ST	6 months	Stanley et al,[53] 1996

Table II. Generalized anxiety disorder: cognitive behavior therapy (CBT) versus other therapies. ST, supportive therapy.

pharmacotherapies (14% versus 32%). The attrition rate was uniformly low. Follow-up results were only available for BT and EMDR: outcome was maintained at 15-week follow-up.

Psychodynamic therapy and hypnotherapy in PTSD

Brom et al's[58] randomized study compared systematic desensitization with psychodynamic therapy, hypnotherapy, and a waiting-list control in 112 patients. The results showed a reduction in symptoms in all three groups at posttest: improvement rate was 41% for systematic desensitization, 34% for hypnotherapy, and 29% for psychodynamic therapy. The between-group difference was nonsignificant. The study had no follow-up.

Debriefing for PTSD prevention

DSM-IV[44] considers that 1 month of stress reaction is required to make a diagnosis of acute PTSD, and 6 months for chronic PTSD. Many subjects present spontaneous remissions in the 1-month interval following the trauma. Debriefing was introduced by Mitchell[59] as a short-term early intervention, which takes place in the immediate aftermath of the trauma (within 48 h). The aim is to reduce immediate posttraumatic distress and to prevent PTSD occurring through discussing and reliving the traumatic event step by step. Debriefing consists of a single group or individual session that lasts 3 h. Typically, seven stages are implemented by a psychologist or in some cases by laypersons in a didactic format that progressively reaches the emotional core of the trauma: "introduction," "facts," "thoughts," "reactions," "symptoms," "teaching," and "relating."
Debriefing has been strongly advocated and widely used in many countries, but well-designed evaluative studies come out with negative outcomes. A meta-analysis of 11 high-quality RCTs was carried out[60] and found that single-session debriefing did not reduce distress, depression, or anxiety, and did not prevent PTSD from occurring. Moreover, the risk of developing PTSD was higher in those patients who received debriefing, compared with those who did not, in one important trial. In conclusion, the authors stated that compulsory debriefing should cease. It seems that debriefing sensitizes the patients, rather than enhancing habituation process. It may also represent a second trauma that "prints" the event in the autobiographical memory. Patients with ruminations seem more likely to have negative reactions.

Obsessive-compulsive disorder

CBT in OCD

Methods

The main behavioral strategy is in vivo exposure with response prevention, which was initiated by Janet[5] and developed by Meyer[61] and Marks.[8] Exposure with response prevention means that exposure is carried out while compulsions are not allowed to the patient. The aim is to reach habituation to obsession-triggering stimuli. Nonetheless, it is less time-consuming and very cost-effective to give homework assignments, which are agreed on with the patient. It is also helpful to involve the patient's partner as a cotherapist. For patients for whom the trigger is more internal, eg, fear of internal representation rather than environmental cues or having covert rituals, prolonged exposure in imagination is the recommended procedure.
A cognitive behavioral model for OCD was proposed by Salkovskis.[62] First, the intrusive thought, which is unacceptable and egodystonic, is viewed as a "normal" process failing to habituate for biological and/or psychological reasons. Second, the obsessive thought (automatic thought) is an evaluation of the intrusive ideas through overresponsibility schemata deep-seated in the long-term memory. This leads to rituals (overt behavior) and neutralizing thoughts (covert behavior), which represents an attempt to control and suppress intrusive thoughts. Such neutralizations prevent habituation to intrusive thoughts from occurring. Hence, Salkovskis proposed a triple intervention: cognitive exposure to intrusive thoughts with neutralization prevention, Socratic questioning of the automatic thoughts and overresponsibility schemata, followed by behavioral experiments (in vivo exposure) to disconfirm the schemata. Treatment classically involves 20 to 25 sessions.

Results of BT

BT has been clearly demonstrated to be superior to placebo and relaxation. The outcome with BT is close to that of serotonergic antidepressants, which have detrimental side effects and a high relapse rate after with-

drawal.[8] The limitations of BT could be summed up as follows: dropout or refusals 25%; no or poor effect 25%; and relapse 20% (3 months to 3 years). The controlled studies combining BT with antidepressants show a better outcome on rituals and depression in the long term. In particular, Cottraux et al[63,64] showed fluvoxamine plus BT compared with placebo plus BT to give better results at 3 months on rituals and at 6 months on depression with equivalent results at 12 and 18 months. The outcomes of the combination studies are summarized in *Table III*.[63-70]

Study	Patients (n)	Hamilton Depression Scale (17 items)	Outcome
Solyom and Sookmann,[65] 1977	27		• *Short term* (6 weeks) CMI = imaginal flooding (ruminations) CMI > thought stopping (ruminations) CMI < E (rituals)
Marks et al,[66] 1980	40	17	• *Short term* (7 weeks) CMI + E > CMI + R
	37		• *Long term* (2 years) CMI + E > PBO + E at weeks 7 to 18, waning at week 36
Marks et al,[67] 1988	49	10	• *Short term* (17 weeks) CMI + E >> CMI + A
	39		• *Long term* (2 years) CMI + E > PBO + E at week 8, waning at week 17
Cottraux et al,[63] 1990	60	19	• *Short term* (8 weeks) FLV + E or FLV > PBO + E (rituals)
	44		• *Mid term* (24 weeks) FLV + E or FLV > PBO + E (depression)
	37		• *Long term* (1 year) FLV + E = PBO + E = FLV
Cottraux et al,[64] 1993	33		• *Long term* (18 months) FLV + E = PBO + E = FLV • *Still under antidepressants* PBO + E and FLV + E = 18% versus FLV = 60% (P<0.05)
Foa et al,[68] 1992	19	20	• *Short term* (6 weeks) IMI > PBO (depression)
			• *Long term* (2 years)
	19	11	IMI + E = PBO + E
	19	20	IMI + E = PBO + E
Baxter et al,[69] 1992	18	9	• *Short term* (10 weeks) FLUOX = E on symptoms and reduction of right caudate hypermetabolism (PET)
Van Balkom,[70] 1994	104		• *Short term* FLV = CBT > WL (rituals) CBT > FLV > WL (anxiety)

Table III. Obsessive-compulsive disorder: exposure with response prevention and antidepressants. A, anti-exposure; CBT, cognitive behavior therapy; CMI, clomipramine; E, exposure; FLUOX, fluoxetine; FLV, fluvoxamine; IMI, imipramine; WL, waiting list; PET: positron emission tomography; PBO, placebo; R, relaxation.

Long-term follow-up of CBT

When addressing the long-term follow-up question, O'Sullivan and Marks[16] reviewed 9 cohorts of patients over 1 to 6 years (mean of 3 years). They found 9% dropout and 78% improvement, with a 60% mean reduction in rituals. Nonetheless, residual symptoms were a rule and liability for depression remained unchanged.

Meta-analysis of CBT

Now that BT is firmly established, several meta-analyses have been carried out. The latest meta-analysis[71] included 77 studies with 4651 patients and showed that BT was superior to SSRI antidepressants as a class. Nevertheless, this difference should be taken with caution as BT is limited by the problem of availability, accessibility, and third-party payment in many countries.

CT in OCD

The status of CT is still under investigation and there have recently been some new studies published *(Table IV)*.[72-79] To date, the usefulness of CT for OCD has been assessed in 8 controlled studies. Emmelkamp et al[72] did not find a superior effect when adding cognitive modifications to in vivo exposure. Nevertheless, the design of the experiment aimed at teaching the patient to replace negative thoughts by positive ones. This could have been used as neutralizing thoughts. Emmelkamp et al[73] compared CT without exposure to self-managed exposure. Six months after the end of treatment, both groups showed equivalent reduction in rituals, generalized anxiety, and social anxiety. Only the cognitive group showed change on the measures of depression. In a study with a more impaired population, Emmelkamp and Beens[74] found similar results at a 6-month follow-up. Van Oppen et al[75] randomized 71 patients in either Beckian CT or exposure. After 16 sessions, they found a superiority of cognitive interventions over exposure. Danger schemata were better modified by CT than with exposure. Unfortunately, this study had no long-term follow-up. A multicentered study (76) compared CT with intensive BT. Sixty-five ambulatory patients with *DSM-IV* OCD and without major depression were randomized into two groups for a 16-week psychological treatment: either CT, or exposure and response prevention, for a 4-week intensive treatment period followed by a maintenance phase of 12 weeks. No medication was prescribed. At week 16, the rates of responders were comparable in the two groups. Depression (bipolar type I) was significantly more improved in the group that received CT. At weeks 26 and 52, improvement was retained in both groups without a between-group difference. Cognitive measures of obsessions changed equally in the two groups. This study replicated on a larger scale the findings of Emmelkamp and coworkers.[73,74]
Freeston et al[77] presented a study comparing a waiting list with a group treated with CBT. In a group of OCD

Study	Outcome
• *CT versus BT (ERP)*	
Emmelkamp et al,[72] 1980	Self-instructional training + ERP = ERP (follow-up 6 months)
Emmelkamp et al,[73] 1988	CT = ERP on rituals
	CT > ERP on depression (follow-up 6 months)
Emmelkamp and Beens,[74] 1991	CT = ERP (follow-up 6 months)
Van Oppen et al,[75] 1995	CT > ERP (posttest)
Cottraux et al,[76] 2001	CT = ERP on rituals
	CT > ERP on depression (posttest)
• *Comparison with a waiting list*	
Freeston et al,[77] 1997	In pure obsessions: CBT > waiting list (follow-up 6 months)
Jones and Menzies,[78] 1998	CT > waiting list at posttest only. No difference at 3-month follow-up
• *Comparison with SSRI (fluvoxamine antidepressant)*	
Van Balkom et al,[79] 1998	ERP, CT, or SSRI combined with ERP or CT: same positive outcomes at 16 weeks
	Active treatments better than a waiting list at week 8

Table IV. Cognitive therapy (CT) in obsessive-compulsive disorder: controlled studies. BT, behavior therapy; CBT: cognitive behavior therapy; ERP: exposure and response prevention; SSRI, selective serotonin reuptake inhibitor.

patients with exclusively covert rituals, that the superiority of CBT over the waiting list was maintained at 6 months' follow-up. Jones and Menzies[78] found that CT was superior to a waiting list at posttest only. Only one study dealt with the problem of combination of CBT with SSRI fluvoxamine[79] and found no difference between active conditions *(Table IV)*.
In conclusion, although there is still is a clear need for more controlled studies, there is good evidence in favor of a positive effect for the cognitive approach in OCD.

Psychodynamic therapy for OCD

There is a dearth of controlled data in this field. An uncontrolled study by Kringlen[80] found that 20% of OCD patients improve during an interval ranging from 13 to 20 years versus 21% of the patients treated with psychoanalytic therapy during the same interval.

Psychosurgery

Since the introduction of prefrontal leukotomy by Moniz,[81] several techniques have been developed: stereotactic leukotomy, stereotactic cingulotomy,[68,69] and the gamma-knife radiosurgery technique of capsulotomy. In general, the orbitofrontal and cingulate regions are the targets for intervention.[82] However, the literature only reports series of uncontrolled case studies. About 25% of a panel of 33 patients who presented an intractable OCD responded in the long term.[83] The side effects are severe—epilepsy, personality disorders, and depression—and there have been cases of suicide.[84-86] Even the gamma-knife, which was supposed to be more precise and safer, presented detrimental effects in the form of extensive local brain necrosis after irradiation.[87] There is obviously a lack of scientific evidence for a durable effect of these techniques in a sizeable number of severe patients. Ethical problems, low effectiveness, and side effects explain why psychosurgical decisions are under the control of ethical committees in most of the countries.

Transcranial stimulation

There is quite limited preliminary evidence that repetitive transcranial magnetic stimulation of prefrontal areas may improve compulsive urges, which were increased after midoccipital stimulations.[88] There was no difference between right and left brain prefrontal stimulations.[89] These experiments were uncontrolled carried out in severe OCD. A positive transient response was found in only 25% of patients.

Social phobia

CBT in social phobia

Methods

Early behavioral interventions were based either on systematic desensitization or assertiveness training. Social skills deficit was hypothesized as being at the core of performance anxiety and social phobia. SST through role play with rehearsal, shaping, and modeling by the therapist was shown to be effective in treating social phobic patients in the early seventies.
A move towards a cognitive model was the next step. According to the cognitive model of social phobia,[90] cognitive factors may be particularly important in the development and maintenance of the negative emotions and avoidance behaviors in social phobic patients. The patients assume that other people are inherently critical, and attach particular importance to being negatively appraised by others. This could be related to a basic cognitive schema of inferiority.[91] CT consists in identifying negative automatic thoughts and schemata, and then modifying them by more realistic interpretations. Current therapeutic models tend to mix cognitive and behavioral methods. The patient's evidence for his or her negative belief is cognitively questioned, but emphasis is also put on behavioral experiments to test the irrational assumptions. Treatment classically involves about 15 to 20 sessions in individual and/or group.

Outcomes

The effectiveness of BT on various types of social anxiety has been demonstrated in several controlled trials. Social phobia, as such, attracted the interest of clinical researchers after its inclusion in *DSM-III*,[42-44] and was studied in controlled trials of SST, systematic desensitization, and in vivo exposure.[92,93] CT, too, demonstrated its effectiveness in studies using waiting list or other therapies as control.[94-96] Two studies reported some advantages of CT combined with exposure over exposure alone,[97,98] while one did not.[99] Another study[100]

found, in a mixed sample of socially inadequate and phobic patients, that role playing and exposure were superior to cognitive restructuring at a 6-month follow-up.
Some researchers noticed that the gains of exposure therapy were often limited by the negative influence of cognitive factors that impeded anxiety reduction.[101] To deal with this problem, a study[102] designed a Cognitive Behavioral Group Treatment (CBGT), which was compared with a credible placebo: lectures and ST. At a 6-month follow-up, CBGT demonstrated clearly higher effects: 75% of the patients in CBGT were improved versus 40% of those in ST. This was confirmed in follow-ups ranging between 4 and 6 years.[103]
A dismantling study[104] comparing CBGT with exposure found that each of the two methods was superior to a waiting list, with a slight advantage of exposure over CT on some measures. The rate of responders was not statistically different in the two active conditions. Surprisingly, there was no greater improvement on cognitive measures in the CBGT group. At a 6-month follow-up there was no longer any between-group difference.
Another trial[105] showed, in limited social phobias, that CT followed by exposure, exposure followed by CT, or the combination of both had the same positive effects without significant difference at a 3-month follow-up. The same authors[106] demonstrated that CT followed by exposure was better than their combination or exposure followed by CT in generalized social phobia, at a 3-month follow-up.
A meta-analysis[107] of 12 CBT and 9 exposure studies concluded that CBT did not yield better outcomes than exposure therapy, on self-report measures of social anxiety, cognitive symptoms, and depressed/anxious mood, at posttest and follow-up.
Another meta-analysis[108] included 42 treatment outcome trials and tested 6 conditions: waiting list, placebo, exposure, CT, CT plus exposure, and SST. All the interventions, including placebo, produced larger effect sizes than a waiting list and did not differ in dropout proportions (12% to 18%). However, only CT associated with exposure yielded an effect size that was larger than placebo (1.06 versus 0.48, respectively). Exposure alone had an effect size of 0.81, nonsignificantly different from placebo. Effect sizes tended to improve at follow-ups.
CBT effectiveness was confirmed by Gould's meta-analysis[109] in which pharmacotherapy (11 studies) had an effect size of 0.62 versus placebo, while CBT (16 studies) reached 0.74 compared with control conditions.
In summary, meta-analytic approaches of the research suggest that CBT is effective and exposure is a crucial component of CBT, while the effect of CT remains in discussion.

Medication and CBT in social phobia

Main outcome studies

Buspirone was less effective than CBT at 6 weeks in reducing performance anxiety in musicians.[110] Gelernter et al[111] compared four groups: CBT, phenelzine, alprazolam, and placebo. All four groups received instruction of self-exposure. All groups improved significantly at 2 months with few differences between them. However, this equal improvement could have resulted from the exposure instructions. BT was superior to atenolol at 3 and 6 months.[112] A positive combination of exposure with sertraline was found at 24 weeks. Combination was superior to placebo, but equal to sertraline alone.[113] Few differences, but in favor of clonazepam, were found in a comparison of this BDZ with behavioral group therapy[114]; patients were only rated at 4, 8, and 12 weeks.
CBGT was found to be superior to pill-placebo and educational group therapy, but slightly inferior to phenelzine on some measures at the 12 weeks' evaluation in a randomized trial.[115] Follow-up data found that, after withdrawal of the medication, CBGT was better, especially in generalized social phobia.[116]

Meta-analysis of CBT and medication

A meta-analysis[117] of psychological and pharmacological treatments for social phobia was conducted: 108 treatment-outcome trials were entered in this meta-analysis. Eleven treatment conditions were compared: waiting-list control, pill placebo, BDZ, SSRIs, monoamine oxidase inhibitors, attention placebo, exposure, cognitive restructuring, and applied relaxation. The most consistently effective treatments for social phobias were pharmacotherapies. BDZs and SSRIs were equally more effective than control conditions. Dropout rates were similar among all the active treatment conditions. The durability of treatment gains for pharmacotherapies was not assessed because of an insufficient number of drug studies with follow-up data. The treatment gains of

CBT, although moderate, continued during the follow-up period. BDZs and SSRIs seem to be effective treatments for social phobia, at least in the short term. The authors recommended assessment of the long-term outcome and evaluation of the inclusion of a CBT during the drug-tapering period.

Psychoanalytic therapies in performance anxiety

A randomized study by Paul[118] in 1966 in students with lack of social skills and a fear of speaking in public showed the superiority of systematic desensitization over a control (attention-placebo) and psychodynamic therapy at a 2-year follow-up. Psychodynamic therapy demonstrated no better outcomes than the waiting list. Although the study recruited a sample of students and the *DSM* criteria for social phobia were not used in those days, Paul's[118] study suggests a significant positive effect of systematic desensitization, and a lack of effectiveness of psychodynamic therapy, in performance anxiety.

Supportive therapy

One trial[119] dealt with a comparison of ST with CBT. The aim of the trial was to study the effectiveness of CBT versus ST carried out "as usual." Sixty-seven *DSM-IV* social phobic patients were randomly allocated into two groups. Group 1 (CBT) received eight 1-hour sessions of individual CT for 6 weeks, followed by six 2-hour sessions of SST in group weekly. Group 2 received ST for 12 weeks (six 30-minute sessions), and then the patients were switched to CBT. No medication was prescribed. At week 6, after CT, group 1 was better than group 2 on the main social phobia measure. At week 12, after SST, group 1 was better than group 2 on most of the measures and demonstrated a significantly higher rate of responders. This finding was replicated after switching group 2 to CBT. Sustained improvement was observed in both groups at follow-up. In summary, CBT was more effective than ST and had long-lasting effects.

Sympathectomy for ereuthophobia

Endothoracic sympathectomy has been carried out for the fear of blushing[120] with a questionable rationale assuming that emotional response is mainly a peripheral problem.[121] Despite early claims of high rate of success, follow-up studies were less optimistic: 67% of the patients had compensatory sweating, 50% gustatory sweating, and Horner's syndrome in 2.5%. Moreover, the number of initially satisfied patients declined over time from 98% to 66%.[122] The survey was made through a simple questionnaire. There was no control group. It is obvious that this is not a treatment of choice for an anxiety problem related to a fear of blushing, more than to real blushing.

Specific phobias

CBT methods for specific phobias

Simple phobia is often considered as a normal fear, like the fear of animals or of blood. Nevertheless, it affects 7% of the general population. In some cases, anxiety and avoidance behaviors become a handicap severe enough to lead to consultation. Treatment classically involves about 10 to 15 sessions of exposure and imagination and/or in vivo and cognitive restructuring.

Outcomes

There is a lack of controlled studies. In many controlled trials, simple phobias are often part of mixed samples of phobic patients. Follow-up studies showed a 54% improvement from baseline, which is maintained at follow-up ranging from 1 to 5 years with BT.[16] Early controlled studies of CT showed negative results.[123,124] A study by Getka and Glass[125] compared four groups for dentist phobia: systematic desensitization, CT and stress management, interview with a warm practitioner prior to intervention, and waiting list. At 1-year follow-up, BT and CT produced equivalent results and were superior to the two other conditions, but this needs more investigation. Virtual reality was introduced as a tool to expose height and flying phobias with positive results in a controlled study of low statistical power.[126] To summarize, despite a scarce literature, in vivo exposure seems the treatment of choice for simple phobia,[127] while pharmacology has not been demonstrated to have positive effects.[128]

Conclusion

This review shows that CBT has been proven to be effective in all the *DSM-IV* categories of anxiety disorders, in numerous RCT and several meta-analyses. Other forms of psychotherapy either have not been tested, or

generally have lesser effects than CBT in RCTs. Surgical approaches proposed for OCD and ereuthophobia are of limited value and may have detrimental side effects, without mentioning their lack of scientific evidence. However, some words of caution may temperate this positive picture of CBT for anxiety disorders.

The cost-containment issues led the procedures to become increasingly simplified. Some attempts have been made to turn many techniques into self-help procedures, or computer-assisted therapy, or therapy administered by nurses, social workers, counselors, priests, or lay people, using treatment manuals. However, manualized therapies have limitations, especially when the therapists are facing patients with multiple *DSM* Axis I and Axis II problems. Those patients represent at least 50% of the referrals in anxiety disorder units. There is obviously a limit to simplification: computer-administered treatment appeared less effective than therapist-administered treatment in OCD.[129]

There are no conflicting issues between biological and psychological theoretical explanations. In practice, the combination of CBT with antidepressants has been shown to be effective in panic disorder and OCD. However, theories and practice may be in competition. CBT, due to the limited number of practitioners, even in developed countries, can be difficult to find. One of the reasons for this limited accessibility rests on the reduced CBT training opportunities in the faculties of medicine and psychology in many countries. Medication is easier to administer, hence it tends to be the first line of intervention, despite the demonstrated efficacy and long-term effectiveness of CBT, and the fact that after stopping medication most of the patients relapse while the outcomes of CBT are stable. In the long-term, CBT costs less than medication, as it prevents relapses from occurring, as shown by cost-effectiveness surveys.[130]

Another stumbling block is the gap between basic research and practice. CBT practice is far ahead of theoretical explanations. Since the adoption of empiricism in the study of normal and abnormal psychology, we should note that the interest in fundamental psychology has tended to fade away. The first behaviorists relied heavily on basic research works, but the gap between practice and basic sciences has grown larger.

Marks[131] recently pointed out that, as far as clinical effectiveness and efficiency are concerned, CBT is coming of age, but it is a toddler in terms of the scientific explanations of its effects. Historically, CBT was the first evidence-based treatment for anxiety disorders, long before evidence-based medicine was a bandwagon,[132] but now needs to be more empirically grounded. Filling this gap will be the endeavor of the 21st century researchers dedicated to the psychological approaches to anxiety disorders. ❑

REFERENCES

1. Ost LG, Westling B, Hellström K. Applied relaxation, exposure in vivo and cognitive methods in the treatment of panic disorder with agoraphobia. *Behav Res Ther*. 1993;31:383-394.
2. Ost LG, Westling B. Applied relaxation vs cognitive behavior therapy in the treatment of panic disorder. *Behav Res Ther*. 1995;33:145-158.
3. Ost LG, Westling B. Applied relaxation vs cognitive behaviour therapy in the treatment of panic disorder. *Behav Res Ther*. 1995;33:145-158.
4. Perroud M. Note sur l'agoraphobie. *Lyon Médical*. 1873;11:80-90.
5. Janet P. *Les obsessions et la psychasthénie*. Paris, France: Alcan; 1903.
6. Freud S. *Lines of Advance in Psychoanalytical Psychotherapy. 1919*. Standard edition, vol 17. London, UK: Hogarth Press; 1955:157-158.
7. Wolpe J. *The Practice of Behavior Therapy*. 2nd ed. New York, NY: Pergamon Press; 1973.
8. Marks I. *Fears, Phobias, and Rituals: Panic, Anxiety, and their Disorders*. New York, NY: Oxford University Press; 1987.
9. Barlow D, Craske MG. *Mastery of your Anxiety and Panic*. Albany, NY: Graywind Publication; 1989.
10. Mattick R, Andrews G, Hadzi-Pavlovic D, et al. Treatment of panic and agoraphobia: an integrative view. *J Nerv Ment Dis*. 1990;178:567-576.
11. Cox BJ, Endler NS, Lee PS, Swinson RP. A meta-analysis of treatments for panic disorder with agoraphobia: imipramine, alprazolam and in vivo exposure. *J Behav Ther Exp Psychiatry*. 1992;23:175-182.
12. Clum GA, Clum G, Surls RA. Meta-analysis of treatments for panic disorder. *J Consult Clin Psychol*. 1993;61:317-326.
13. Van Balkom AJLM, Bakker A, Spinhoven P, Blaauw B, Seemk S, Ruesink B. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral and combination treatments. *J Nerv Ment Dis*. 1997;185:510-516.
14. Bakker A, Van Balkom A, Spinhoven P, Blaauw B, Van Dyck R. Follow-up on the treatment of panic disorder with or without agoraphobia. A quantitative review. *J Nerv Ment Dis*. 1998;186:414-419.
15. Gould RA, Otto MW, Pollack MH. A meta-analysis of treatment outcome for panic disorder. *Clin Psychol Rev*. 1995;8:819-844.
16. O'Sullivan G, Marks I. Long-term outcome of phobic, and obsessive-compulsive disorders after treatment. In: Noyes R, Roth M, Burrows GD, eds. *Handbook of Anxiety. Vol 4. The Treatment of Anxiety*. Amsterdam, The Netherlands: Elsevier; 1990.
17. Zitrin C, Klein D, Woerner M. Treatment of agoraphobia with group in vivo exposure and imipramine. *Arch Gen Psychiatry*. 1980;37:63-72.
18. Telch M, Agras S, Barr-Taylor C, et al. Combined pharmacological and behavioral treatment for agoraphobia. *Behav Res Ther*. 1985;22:325-335.
19. Agras S. Behaviour therapy and psychopharmacology. Combined pharmacological and psychological treatment of panic disorder: current status and future direction. In: Wolf BE, Maser JD. *Treatment of Panic Disorder*. Washington DC: American Psychiatric Press; 1994.
20. de Beurs E, van Balkom A, Lange J, Koele P van Dyck R. Treatment of panic disorder with agoraphobia: comparison of fluvoxamine, placebo, and psychological panic management combined with exposure and of exposure in vivo alone. *Am J Psychiatry*. 1995;152:683-691.

Tratamientos no farmacológicos para los trastornos de ansiedad

Se presenta una revisión basada en la evidencia de los tratamientos no farmacológicos para los trastornos de ansiedad. Gran parte de la investigación controlada está dedicada a la terapia cognitivo conductual (TCC) y muestra su eficiencia y eficacia en los meta-análisis para todos los trastornos de ansiedad de la IV Edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-IV). En unos pocos estudios controlados se ha examinado la relajación, las terapias psicoanalíticas, la terapia Rogeriana no directiva, la hipnoterapia y la terapia de apoyo, lo que impide cualquier conclusión definitiva acerca de su eficacia en fobias específicas, agorafobia, trastorno de pánico, trastorno obsesivo compulsivo (TOC) o trastorno por estrés postraumático (TEPT). La TCC fue claramente mejor que la terapia psicoanalítica para el trastorno de ansiedad generalizado (TAG) y para la angustia de rendimiento. El debriefing psicológico para el TEPT resultó perjudicial para los pacientes en un meta-análisis de alta calidad. Estudios no controlados de técnicas de psico-cirugía para el TOC intratable demostraron un éxito limitado y efectos laterales indeseables. Se obtuvieron resultados similares para la simpatectomía en la ereutofobia. La neuroestimulación transcraneal para el TOC está en una fase preliminar de estudio. Se discuten los problemas teóricos y prácticos de la propagación de la TCC.

Traitements non pharmacologiques des troubles anxieux

Il est présenté ici une revue basée sur les preuves des traitements non pharmacologiques des troubles anxieux. La grande majorité de la recherche contrôlée est consacrée à la thérapie cognitivocomportementale (TCC) et des métaanalyses on montré la pertinence et l'efficacité de cette thérapie dans tous les troubles anxieux du Manuel diagnostique et statistique des troubles mentaux (DSM-IV)*. La relaxation, les thérapies psychoanalytiques, la thérapie non directive dite de « Rogers », l'hypnothérapie, et les thérapies de soutien ont été examinés dans quelques études contrôlées, qui écartent toute conclusion définitive sur leur efficacité dans les diverses formes de phobie, l'agoraphobie, le trouble panique, le trouble obsessionnel compulsif (TOC), et l'état de stress posttraumatique (ESPT). La TCC était manifestement plus efficace que le traitement psychanalytique dans les troubles anxieux généralisés (TAG) et l'anxiété de performance. Le « debriefing » psychologique pour l'ESPT est apparu dommageable aux patients dans une métaanalyse de haute qualité. Des études non contrôlées des techniques de psychochirurgie pour les TOC rebelles ont démontré un succès limité et des effets secondaires fâcheux.* Idem *pour la sympathectomie dans l'éreuthophobie. La neurostimulation transcrânienne pour les TOC a fait l'objet d'études préliminaires. Les problèmes théoriques et pratiques pour la diffusion de la TCC sont discutées.*

21. Oehrberg S, Christiansen PE, Behnke K, et al. Paroxetine in the treatment for panic disorder. A randomised, double-blind, placebo-controlled trial. *Br J Psychiatry*. 1995;167:374-379.

22. Sharp DM, Power KG, Simpson RJ, et al. Fluvoxamine, placebo and cognitive behaviour therapy used alone and in combination in the treatment of panic disorder and agoraphobia. *J Anxiety Disord*. 1996;4:219-242.

23. Barlow HD, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA*. 2000;283:2529-2536.

24. Solyom C, Solyom I, LaPierre Y, et al. Phenelzine and exposure in the treatment of phobias. *Biol Psychiatry*. 1981;16:239-247.

25. Marks I, Gray S, Cohen D, Hill R, Mawson D, Ramm L, Stern R. Imipramine and brief therapist aided exposure in agoraphobics having self-exposure homeworks. *Arch Gen Psychiatry*. 1983;40:153-161.

26. Mavissakalian M, Michelson L. Agoraphobia: relative and combined effectiveness of therapist-assisted in vivo exposure and imipramine. *J Clin Psychiatry*. 1986;47:117-122.

27. Fahy TJ, O'Rourke D, Brophy J, et al. The Galway study of panic disorder: clomipramine and lofepramine in *DSM-3-R* panic disorder. A placebo-controlled trial. *J Affect Disord*. 1992;25:63-76.

28. Loerch B, Graf-Morgenstern M, Hautzinger M, et al. Randomised placebo-controlled trial of moclobemide, cognitive-behavioural therapy and their combination in panic disorder with agoraphobia. *Br J Psychiatry*. 1999;174:205-212.

29. Marks I, Swinson R, Basoglu M, et al. Alprazolam and exposure alone or combined in panic disorder with agoraphobia: a controlled study in London and Toronto. *Br J Psychiatry*. 1993;162:776-787.

30. Wardle J, Hayward P, Higgit A, et al. Effects of concurrent diazepam treatment on the outcome of exposure therapy in agoraphobia. *Behav Res Ther*. 1994;32:203-215.

31. Cottraux J, Note ID, Cungi C, et al. A controlled study of cognitive-behavior therapy with buspirone or placebo in panic disorder with agoraphobia. A one-year follow-up. *Br J Psychiatry*. 1995;167:635-641.

32. Otto M, Pollack MH, Sachs G, et al. Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. *Am J Psychiatry*. 1993;150:1485-1490.

33. Spiegel D, Bruce T, Gregg B, et al. Does cognitive behavior therapy assist slow-taper alprazolam discontinuation in panic disorder? *Am J Psychiatry*. 1994;151:876-881.

34. Barlow D, Craske M, Cerny J, et al. Behavioral treatment of panic disorder. *Behav Ther*. 1989;20:261-282.

35. Craske M, Brown T, Barlow D. Behavioral treatment of panic disorder: a two-year follow-up. *Behav Ther*. 1991;22:289-304.
36. Clark D, Salkovskis P, Hackmann A, Middleton H, Anastasiades P, Gelder M. A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. *Br J Psychiatry*. 1994;164:759-769.
37. Ost LG. Applied relaxation versus progressive relaxation in the treatment of panic disorder. *Behav Res Ther*. 1988;26:13-22.
38. Arntz A, Van den Hout M. Psychological treatment of panic disorder without agoraphobia: cognitive therapy versus applied relaxation. *Behav Res Ther*. 1996;34:113-121.
39. Beck AT, Sokol L, Clark DA, et al. A cross-over of focused cognitive therapy for panic disorder. *Am J Psychiatry*. 1992;149:778-783.
40. Shear K, Pilkonis P, Cloitre M, et al. Cognitive-behavioral treatment compared with nonprescriptive treatment of panic disorder. *Arch Gen Psychiatry*. 1994;51:395-401.
41. Wiborg IM, Dahl AA. Does brief dynamic therapy reduce the relapse rate of panic disorder. *Arch Gen Psychiatry*. 1996;53:689-694.
42. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
43. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, revised. Washington, DC: American Psychiatric Association; 1987.
44. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
45. Wells A. *Cognitive Therapy for Anxiety Disorders. A Practice Manual and Conceptual Guide*. Chichester, UK: John Wiley and Sons; 1997.
46. Gould RA, Buckminster S, Pollack MH, Otto MW, Yap L. Cognitive-behavioral and pharmacological treatment for social phobia: a meta-analysis. *Clin Psychol Sci Pract*. 1997;4:291-306.
47. Gould RA, Otto MW, Pollack MH, Yay L. Cognitive behavioural and pharmacological treatment of generalized anxiety disorder: a preliminary meta-analysis. *Behav Ther*. 1997;28:285-305.
48. Durham R, Murphy T, Allan T, Richard K, Treliving L Fenton G. Cognitive therapy, analytic psychotherapy and anxiety management for anxiety management training for anxiety disorder. *Br J Psychiatry*. 1994;165:315-323.
49. White J, Keenan M, Brooks N. Stress control: a controlled comparative investigation of large group therapy for generalized anxiety disorder. *Behav Psychother*. 1992;20:97-114.
50. Borkovec TD, Mathews AM, Chambers A, Ebrahami S, Lytle R, Nelson R. The effects of relaxation training with cognitive or nondirective therapy and the role of relaxation-induced anxiety in the treatment of generalized anxiety. *J Consult Clin Psychol*. 1987;55:883-888.
51. Borkovec TD, Costello E. Efficacy of applied relaxation and cognitive-behavioral therapy in the treatment of generalized anxiety disorder. *J Consult Clin Psychol*. 1993;61:611-619.
52. Blowers C, Cobb J, Mathews A. Generalised anxiety: a controlled treatment study. *Behav Res Ther*. 1987;25:493-502.
53. Stanley MA, Beck JG, Glassco JD. Treatment of generalized anxiety in older adults: a preliminary comparison of cognitive-behavioral and supportive approaches. *Behav Ther*. 1996;27:565-581.
54. Wilson SA, Becker LA, Tinker RH. Eye movement desensitization and reprocessing (EMDR) treatment for psychologically traumatized individuals. *J Consult Clin Psychol*. 1995;63:928-937.
55. Devilly GJ , Spence SH, Rapee R. Statistical and reliable change with eye movement desensitization and reprocessing: treating trauma within a veteran population. *Behav Ther*. 1998:435-455.
56. Marks IM, Lovell K, Noshirvani H, Livanou M, Trasher S. Treatment of posttraumatic stress disorder by exposure and/or cognitive restructuring. *Arch Gen Psychiatry*. 1998;5:317-325.
57. Van Etten ML, Taylor S. Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. *Clin Psychol Psychother*. 1998;5:126-144.
58. Brom D, Kleber RJ, Defares PB. Brief psychotherapy for post-traumatic stress disorders. *J Consult Clin Psychol*. 1989;57:607-612.
59. Mitchell JT. When disaster strikes … the critical incidents stress debriefing process. *J Emerg Med Serv*. 1983;8:36-39.
60. Rose S, Bisson J, Wessely S. Psychological debriefing for preventing post-traumatic stress disorder (PTSD). The Cochrane Library, Issue 3. Oxford, UK: Update Software. http://www.update-software.com/abstracts/ab000560.htm. Accessed 24 July 2002.
61. Meyer V. Modifications of expectations in cases with obsessional rituals. *Behav Res Ther*. 1966;4:273-280.
62. Salkovskis PM. Obsessional-compulsive problems. A cognitive behavioral analysis. *Behav Res Ther.* 1985;23:571-583.
63. Cottraux J, Mollard E, Bouvard M, et al. A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1990;5:17-30.
64. Cottraux J, Mollard E, Bouvard M, Marks I. Exposure therapy, fluvoxamine or combination treatment in obsessive-compulsive disorder: 1-year follow-up. *Psychiatry Res*. 1993;49:63-75.
65. Solyom L, Sookman D. A comparison of clomipramine hydrochloride (Anafranil) and behaviour therapy in the treatment of obsessive neurosis. *J Int Med Res*. 1977;5(suppl 5):49-61.
66. Marks I, Stern RS, Mawson D, Cobb J, McDonald R. Clomipramine and exposure for obsessive-compulsive rituals. *Br J Psychiatry*. 1980;136:1-25.
67. Marks I, Lelliott P, Basoglu M, Noshirvani H, Monteiro W, Kasvikis Y. Clomipramine, self-exposure and therapist-aided exposure in obsessive-compulsive ritualisers. *Br J Psychiatry*. 1988;152:522-534.
68. Foa E, Kozak M, Steketee G, McCarthy PR. Treatment of depressive and obsessive-compulsive symptoms in obsessive-compulsive disorder by imipramine and behaviour therapy. *Br J Clin Psychol*. 1992;31:279-292.
69. Baxter L, Schwartz J, Bergman K, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:681-689.
70. Van Balkom A. *Comparative Treatment Studies in Panic Disorder with Agoraphobia and Obsessive-Compulsive Disorder*. Thesis. Amsterdam, The Netherlands: Vrije Universiteit Amsterdam; 1994.
71. Kobak KA, Greist JH, Jefferson JW, Katzlenick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive-compulsive disorder. *Psychopharmacology*. 1998;3:205-216.
72. Emmelkamp P, Van der Helm M, Van Zanten B, Plochg I. Contribution of self-instructional training to the effectiveness of exposure in vivo: a comparison with obsessive-compulsive patients. *Behav Res Ther*. 1980;18:61-66.
73. Emmelkamp P, Visser S, Hoekstra RJ. Cognitive therapy versus in vivo exposure in the treatment of obsessive-compulsive patients. *Cogn Ther Res*. 1988;12:103-114.
74. Emmelkamp P, Beens H. Cognitive therapy with obsessive-compulsive disorder: a comparative evaluation. *Behav Res Ther*. 1991;29:293-300.
75. Van Oppen P, de Haan E, Van Balkom AJ, Spinhoven P, Hogduin K, Van Dyck R. Cognitive therapy and exposure in vivo in the treatment of obsessive-compulsive disorder. *Behav Res Ther*. 1995;33:379-390.
76. Cottraux J, Ivan Note I, Yao SN, et al. A randomized controlled trial of cognitive therapy versus intensive behaviour therapy in obsessive-compulsive disorder subjects. *Psychother Psychosomatics*. 2001;70:288-297.
77. Freeston MH, Ladouceur R, Gagnon F, et al. Cognitive-behavioral treatment of obsessive thoughts: a controlled study. *J Consult Clin Psychol*. 1997;65:405-413.
78. Jones MK, Menzies RG. Danger ideation reduction therapy (DIRT) for obsessive-compulsive washers, controlled trial. *Behav Res Ther*. 1998;36:959-970.
79. Van Balkom AJLM, De Haan E, Van Oppen P, Spinhoven P, Hogduin KAL, Van Dyck R. Cognitive and behavioral therapies alone or in combination with fluvoxamine in the treatment of obsessive-compulsive disorder. *J Nerv Ment Dis*. 1998;186:492-498.`
80. Kringlen E. Obsessional neurotics: a long-term follow-up. *Br J Psychiatry*. 1965;111:709-722.
81. Moniz E. Prefrontal leucotomy in the treatment of mental disorder (May, 1937). *Am J Psychiatry*. 1994;151:237-239.
82. Ballantine H, Bouckoms A, Thomas E, Giriunas I. Treatment of psychiatric illness by stereotaxic cingulotomy. *Biol Psychiatry*. 1987;22:807-819.
83. Baer L, Rauch S, Ballantine T, et al. Cingulotomy for intractable obsessive-compulsive disorder. Prospective long-term follow-up of 18 patients. *Arch Gen Psychiatry*. 1995;52:384-392.
84. Mindus P, Rasmussen SA, Lindquist C. Neurosurgical treatment for refractory obsessive-compulsive disorder: implications for understanding frontal lobe function. *J Neuropsychiatry Clin Neurosci*. 1994;6:467-477.
85. Hay P, Sachdev P, Cumming S, Smith JS, Kitchener P, Matheson J. Treatment of obsessive-compulsive disorder by psychosurgery. *Acta Psychiatr Scand*. 1993;87:197-207.

86. Jenike MA, Baer L, Ballantine T, et al. Cingulotomy for refractory obsessive-compulsive disorder. A long-term follow-up of 33 patients. *Arch Gen Psychiatry*. 1991;48:548-555.
87. Kihkström L, Guo WY, Lindquist C, Mindus P. Radiobiology of radiosurgery for refractory anxiety disorders. *Neurosurgery*. 1995;36:294-302.
88. Greenberg BD, George MS, Martin JD, et al. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry*. 1997;154:867-869.
89. Sachdev PS, McBride R, Loo CK, Mitchell PB, Malhi GS, Croker VM. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. *J Clin Psychiatry*. 2001;62:981-984.
90. Beck AT, Emery G, Greenberg R. *Anxiety Disorders and Phobias. A Cognitive Perspective*. New York, NY: Basic Books; 1985.
91. Yao SN, Cottraux J, Martin R, et al. Inferiority in social phobics, obsessive-compulsive and non-clinical controls. A controlled study with the inferiority scale. In: Sanavio E, ed. *Behaviour and Cognitive Therapy Today: Essays in Honour of Hans J. Eysenck*. London, UK: Elsevier; 1998.
92. Marzillier J, Lambert C, Kellett J. A controlled evaluation of systematic desensitization and social skills training for socially inadequate psychiatric patients. *Behav Ther Res*. 1976;14:225-238.
93. Butler G, Cullington A, Monby M. Exposure and anxiety management in the treatment of social phobias. *J Clin Psychol*. 1984;52:642-650.
94. Shaw P. A comparison of three behaviour therapies in the treatment of social phobia. *Br J Psychiatry*. 1979;134:620-623.
95. Kanter NJ, Golfried MR. Relative effectiveness of rational restructuring and self-control desensitization in the reduction of interpersonal anxiety. *Behav Ther*. 1979;10:472-490.
96. Emmelkamp PMG, Mersch PP, Vissia E, Van der Helm M. Social phobia: a comparative evaluation of cognitive and behavioural interventions. *Behav Res Ther*. 1985;23:365-369.
97. Jerremalm A, Jansson L, Ost LG. Cognitive and physiological reactivity and the effects of different behavioural methods in the treatment of social phobias. *Behav Res Ther*. 1986;24:171-180.
98. Biran M, Wilson GT. Treatment of phobic disorders using cognitive and exposure methods: a self-efficacy analysis. *J Consult Clin Psychol*. 1981;49:886-899.
99. Mattick R, Peters L, Clarke C. Exposure and cognitive restructuring for social phobia: a controlled study. *Behav Ther*. 1989;20:3-23.
100. Stravinsky A, Marks I, Yule W. Social skills problems in neurotic outpatients. *Arch Gen Psychiatry*. 1982;39:1378-1385.
101. Butler G. Exposure as a treatment for social phobia: some instructive difficulties. *Behav Res Ther*. 1985;23:651-657.
102. Heimberg R, Dodge C, Hope D, Kennedy C, Zollo L. Cognitive behavioural group treatment for social phobia: comparison with a credible placebo control. *Cogn Ther Res*. 1990;14:1-23.
103. Heimberg R, Salzman D, Holt C, Blendell K. Cognitive behavioral group treatment for social phobia: effectiveness a five-year follow-up. *Cogn Ther Res*. 1993;17:325-339.
104. Hope DA, Heimberg RG, Bruch MA. Dismantling cognitive-behavioral group therapy for social phobia. *Behav Res Ther*. 1995;33:637-650.
105. Emmelkamp PMG, Scholing A. Cognitive and behavioural treatments of fear of blushing, sweating or trembling. *Behav Res Ther*. 1993;31:155-170.
106. Scholing A, Emmelkamp PMG. Exposure with and without cognitive therapy for generalized social phobia: effects of individual and group treatment. *Behav Res Ther*. 1993;31:667-681.
107. Feske U, Chambless DL. Cognitive behavioural versus exposure only treatment for social phobia. *Behav Ther*. 1995;26:695-720.
108. Taylor S. Meta-analysis of cognitive-behavioral treatments for social phobia. *J Behav Ther Exp Psychiatry*. 1996;27:1-9.
109. Gould RA, Buckminster S, Pollack MH, Otto MW, Yap L. Cognitive-behavioral and pharmacological treatment for social phobia: a meta-analysis. *Clin Psychol Sci Pract*. 1997;4:291-306.
110. Clark DB, Agras WS. The assessment and treatment of performance anxiety in musicians. *Am J Psychiatry*. 1991;148:598-605.
111. Gerlernter C, Uhde T, Cimbolic P, et al. Cognitive-behavioural and pharmacological treatments of social phobia. A controlled study. *Arch Gen Psychiatry*. 1991;48:938-945.
112. Turner SM, Beidel DC, Jacob RG. Social phobia: a comparison of behavior therapy and atenolol. *J Consult Clin Psychol*. 1994;62:350-358.
113. Blomhoff S, Haug TT, Hellström K, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry*. 2001;179:23-30.
114. Otto MW, Pollack MH, Gould RA, Worthington JJ, McArdle ET, Rosenbaum JF. A comparison of the efficacy of clonazepam and cognitive-behavioral group therapy for the treatment of social phobia. *J Anxiety Disord*. 2000;14:345-358.
115. Heimberg R, Liebowitz M, Hope D, et al. Cognitive behavioral group therapy vs phenelzine therapy for social phobia. *Arch Gen Psychiatry*. 1998;55:1133-1141.
116. Liebowitz RM, Heimberg R, Schneier FR, et al. Cognitive behavioral group therapy versus phenelzine in social phobia: long-term outcome. *Depression Anxiety*. 1999;10:89-98.
117. Fedoroff IC, Taylor S. Psychological and pharmacological treatments of social phobia: a meta-analysis. *J Clin Psychopharmacol*. 2001;21:311-324.
118. Paul G. *Insight Versus Desensitization in Psychotherapy*. Stanford, Calif: Stanford University Press; 1966.
119. Cottraux J, Note I, Albuisson E, et al. Cognitive behaviour therapy versus supportive therapy in social phobia: a randomised controlled trial. *Psychother Psychosomatics*. 2000;69:137-146.
120. Yilmaz EN, Dur AHM, Cuesta MA, Rauwerda JA. Endoscopic versus transaxillary thoracic sympathectomy for primary axillary and palmar hyperhidrosis and/or facial blushing: 5-year experience. *Eur J Cardiothorac Surg*. 1996;10:168-172.
121. Drummond PD, Lance JW. Facial flushing and sweating mediated by the sympathetic nervous system. *Brain*. 1987;110:793-803.
122. Herbst F, Plas EG, Függer R, Fritsch A. Endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limbs: a critical analysis and long-term results of 480 operations. *Ann Surg*. 1994;220:86-90.
123. Ladouceur R. Participant modeling with or without cognitive treatment for phobias. *J Consult Clin Psychol*. 1983;51:942-944.
124. Biran M, Wilson GT. Treatment of phobic disorders using cognitive and exposure methods: a self-efficacy analysis. *J Consult Clin Psychol*. 1981;49:886-899.
125. Getka EJ, Glass CR. Behavioural and cognitive-behavioural approaches to the reduction of dental anxiety. *Behav Ther*. 1992;23:433-448.
126. Rothbaum BO, Hodges LF, Kooper R, Opdyke D, Williford JS, North M. Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. *Am J Psychiatry*. 1995;152:626-628.
127. Rachman SJ. In: Salkovskis PM, ed. *Trends in Cognitive and Behavioural Therapy*. Chichester, UK: John Wiley and Sons Ltd; 1996.
128. Zitrin C, Klein D, Woerner M. Behaviour therapy, supportive psychotherapy, imipramine and phobias. *Arch Gen Psychiatry*. 1978;35:307-316.
129. Greist JH, Marks IM, Baer L, et al. Behavior therapy for obsessive-compulsive disorder guided by a computer or by a clinician compared with relaxation as a control. *J Clin Psychiatry*. 2002;63:138-145.
130. Miller NE, Magruder KM. *Cost-effectiveness of psychotherapy*. Oxford, UK: Oxford University Press; 1999:224-234.
131. Marks IM. The maturing of therapy: some brief psychotherapies help anxiety/depressive disorders but mechanisms of action are unclear. *Br J Psychiatry*. 2002;180:200-204.
132. Salkovskis PM. Empirically grounded clinical interventions: cognitive-behavioural therapy progresses through a multi-dimensional approach to clinical science. *Behav Cogn Psychother*. 2002;30:3-9.

Instructions for authors

AIM AND SCOPE

***Dialogues in Clinical Neuroscience* is a quarterly publication that aims to serve as an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects. Each issue addresses a specific topic, and also publishes free contributions in the field of neuroscience as well as other non–topic-related material.**

GENERAL INSTRUCTIONS

Manuscripts should be provided on word-processor disks (3.5-in, for IBM, IBM-compatible, or Apple computers) with three hard copies (text and figures) printed on one side of standard-sized white bond paper, double-spaced, with 1-inch/2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines; 250 words per page.

All texts should be submitted in English. In the case of translations, the text in the original language should be included.

Provide black and white photograph(s) of author(s).

On the title page, provide: a title (concise and informative); full names of authors (first name, middle name initial, and last name); highest academic degrees (in country-of-origin language); affiliations (names of department[s] and institution[s]) at the time the work was done; a short running title (no more than 50 letters and spaces); keywords (5 to 10); corresponding author's complete mailing address and telephone, fax, and e-mail; acknowledgments.

Provide an abstract in English (125-150 words) (except for Editorials, Posters, and Letters to the Editor). Abstracts that are too short or long will be edited by the editorial department or returned to the author. Abstracts will be translated into French and Spanish by the publisher's editorial department.

Abbreviations should be used sparingly and expanded at first mention. A list of selected abbreviations and acronyms should be provided (or will be prepared by the editorial department) where necessary.

In the text include headings using a consistent style for the various levels of headings, to highlight key points and facilitate comprehension of the text. The editorial department reserves the right to add, modify, or delete headings when necessary.

Use SI units.

Use generic names of drugs.

REFERENCES

All references should be cited in the text and numbered consecutively using superscript arabic numerals. Presentation of the references should be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *Ann Intern Med.* 1997;126:36-47 ("Vancouver style"). The author-date system of citation is not acceptable. "In press" references should be avoided. In the bibliography, titles of journals should be abbreviated according to the *Index Medicus.* All authors should be listed up to six; if there are more, only the first three should be listed, followed by "et al." Where necessary, references will be styled by the editorial department to *Dialogues in Clinical Neuroscience* copyediting requirements. Authors bear total responsibility for the accuracy and completeness of all references and for correct text citation. Example of style for references:

1. Schneider LS, Olin JT, Lyness SA, Chui HC. Eligibility of Alzheimer's disease clinic patients for clinical trials. *J Am Geriatr Soc.* 1997;45:1-6.

2. Dubovsky J, Weber JL, Orr HT, et al. A second gene for familial febrile convulsions maps on chromosome 19p. *Am J Hum Genet.* 1996;59(suppl 1):A223.

3. Carpenter WT Jr, Buchanan RW. Domains of psychopathology relevant to the study of etiology and treatment in schizophrenia. In: Schulz SC, Tamminga CA, eds. *Schizophrenia: Scientific Progress.* New York, NY: Oxford University Press; 1989:13-22.

FIGURES AND TABLES

Submit figures as two sets of clear glossy prints. Figures should be of good quality or professionally prepared, numbered according to their order, with proper orientation indicated (eg, "top" or "left"), and fully explicit legends provided, not repetitive of text. All abbreviations used should be expanded in the legends. As figures and graphs may need to be reduced or enlarged, all absolute values and statistics should be provided. Illustrations will be reproduced in full color only when clearly necessary, eg, images from nuclear medicine or histology. Provide each table on a separate sheet, with title above and description below. All figures and tables should be cited in the text, with distinct numbering for figures and tables.

SPECIFIC FORMATS

Editorial: no more than 400 words.

Pharmacological aspects; Clinical research; Basic research: 3000-5000 words (exclusive of abstract, references, tables, and figure legends).

State of the art: maximum 7000 words (exclusive of abstract, references, tables, and figure legends).

Free papers: no more than 2500 words (exclusive of abstract, references, tables, and figure legends).

Posters / images in neuroscience: take up 2 facing printed pages of the journal. Posters may need to be edited to meet formatting requirements. Legends must be provided with all illustrations.

Letters to the editor: (of no more than 500 words, and including no more than 10 references) are welcomed. Letters will be selected by the Editor, and published according to available space. Unpublished letters will not be returned to the authors.

EDITORIAL ASSESSMENT AND PROCESSING

All contributions to *Dialogues in Clinical Neuroscience* will be reviewed by members of the Editorial Board and submitted to expert consultants for peer review.

All contributions to *Dialogues in Clinical Neuroscience* will be styled by the publisher's editorial department according to the specifications of the current edition of the American Medical Association *Manual of Style* (Williams & Wilkins). Page proofs and editorial queries will be sent to the corresponding author for approval and should be returned within 48 hours by fax and express mail. If this deadline is not met, the changes made by the editorial department will be assumed to be accepted by the author. Authors are responsible for all statements made in their work, including changes made by the editorial department and authorized by the author. Articles and abstracts will be edited to required length or returned to the author if specific requirements are not complied with.

COPYRIGHT

Copyright of articles will be transferred to the publisher of *Dialogues in Clinical Neuroscience.* The Copyright Transfer Agreement must be signed by the main author and all coauthors and returned to the publisher.

For **reproduction of copyrighted work,** the author is required to obtain authorizations from the author(s) (including self) and the publisher(s) and provide copies of these authorizations with the manuscript.

Dialogues
in clinical neuroscience

Dialogues in clinical neuroscience

Contents of latest issues

Editor in Chief: Jean-Paul MACHER

2002 · Volume 4 · No. 2

CNS Aspects of Reproductive Endocrinology

2002 · Volume 4 · No. 3

Anxiety I

Instructions for authors at the back of each issue

For information on this journal contact: Dr Marc-Antoine CROCQ
FORENAP - Institute for Research in Neuroscience and Neuropsychiatry - BP29 - 68250 Rouffach - France
Tel: +33 3 89 78 71 20 / 70 18 - Fax: +33 3 89 78 51 24 - E-mail: macrocq@forenap.asso.fr

If you wish to receive future issues of *Dialogues in Clinical Neuroscience*, please contact
mail.dialneuro@fr.netgrs.com

This publication is supported by an educational grant from Servier

www.servier.com

03 ST 021 BA