EXAMINING THE RELATIONSHIP BETWEEN ANXIETY DISORDERS AND DEPRESSION

Anxious people are often depressed and depressed people are often anxious. What is the relationship between the two?

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It is meaningful to distinguish anxiety and depression both as symptoms and as syndromes (clusters of symptoms that occur together and which may comprise a disorder).

Anxiety, as a symptom, is a feeling of apprehension caused by anticipation of danger, which may be internal or external. It may be free-floating (pervasive but occurring as an unfocused fear not attached to any idea) or specific and situational. It may be present as fear, which is anxiety caused by consciously recognised and realistic danger, or as agitation, which is severe anxiety associated with motor restlessness. Fear is a response to a known external threat; anxiety is a response to a threat that is unknown and internal. Fear tends to be sudden and non-conflictual, anxiety is insidious and conflictual. Depression as a symptom may be defined as psychopathological feelings of sadness. These should be distinguished from ordinary misery or from grief, which is sadness appropriate to loss as part of the bereavement process.

Both anxiety and depression are affects within the normal repertoire of everyone. Both may be ordinary and normal responses which, if they become unduly prolonged, severe and hinder the individual's adaptive or functional capacity, become pathological.

This article looks further at the pathological aspects of anxiety disorders and their relationship to depression. Depression will be considered here both as a symptom and as a syndrome, most commonly major depression (uni- or bipolar) or dysthymia (unless otherwise specified).

Both anxiety disorders and depressive disorders are common: the lifetime prevalence of any anxiety disorder is 1 in 4 and that of major depressive disorder 1 in 6. If these disorders were unrelated, approximately 1 in 24 people in the general population would have both. Epidemiological studies suggest that the co-morbidity is much higher, thus suggesting an intimate connection between them where the presence of one increases the likelihood of the other occurring.

SYMPTOMATIC RELATIONSHIPS

In general, with the experience of anxiety as a symptom, motor and somatic effects may result (as with depression), as well as changes in thinking, perception and learning. Confusion and distortions of thinking and/or perceptions may occur in time, space, person and the meaning of events. These cognitive distortions can interfere with learning by lowering concentration, and by reducing recall and the ability to make associations. Emotions can also affect the selectivity of attention. Anxious persons (and those who are depressed) may select certain environmental elements and overlook others in their effort to prove that they

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are justified in considering the situation frightening. If they falsely justify their fear they enhance their anxiety selectively, setting up a vicious circle of anxious thoughts, distorted perceptions and increased anxiety. If they falsely reassure themselves by selective thinking, then appropriate anxiety may be reduced and they may fail to take the necessary precautions. In both, depression may result.

Patients with panic disorder, with or without agoraphobia, often have depressive symptoms with or without a co-morbid depressive disorder. In addition, patients with a depressive disorder may experience panic attacks when overwhelmed with anxiety. In patients with social phobia it is important to distinguish the fear of embarrassment or humiliation characteristic of this condition from the social withdrawal which commonly occurs in depression owing to the sufferer's negative feelings about him/herself. Further interviews and mental state examinations (MSEs) ought to differentiate other depressive symptoms as part of a co-morbid depressive disorder. However, on MSEs symptoms of depression are commonly found in at least one-third of all phobic patients (specific and social phobia) and may be reactions to chronicity or severity of the phobia. The onset of the disorder may also indicate the direction of causality where depression often follows (but may also precede social avoidance or other anxiety symptoms).

In obsessive-compulsive disorder (OCD), depressive symptoms occur in about 50% of all patients. Social avoidance and secretiveness in OCD may also occur and be mistaken for a primary depressive disorder, although if depression is concomitant these behaviours may be worsened. In patients with post-traumatic stress disorder (PTSD), feelings of guilt, rejection and depression may occur as part of this picture, with impaired memory and attention. In generalised anxiety disorder (GAD) depressive symptoms are common and difficulty in concentrating and easy fatigue may also be taken as part of a depressive disorder. In medical disorders or substance-induced disorders anxiety or depressive symptoms or disorders may also occur, e.g. with cerebrovascular disease, hypoxia, epilepsy, porphyria, cocaine/amphetamines, alcohol dependence, rheumatoid arthritis and vitamin B_{12} deficiency, etc.

In addition, *DSM-IV-TR* (APA, 2000) codes research criteria for a mixed anxiety-depressive disorder. Here, persistent or recurrent dysphoric (unpleasant) mood for at least a month must occur with at least 4 symptoms, namely trouble in concentrating, sleep disturbance, low energy/fatigue, irritability, worry, tearfulness, hypervigilance, pessimism, hopelessness and low self-esteem/feelings of worthlessness. Functional impairment occurs and the disorder is not better explained by substance use, general medical conditions or other mental illness. An equal mixture of anxiety and depressive symptoms occurs and the condition is particularly prevalent in primary care and mental health outpatient settings. The evidence for this disorder is suggested by the high proportion of patients having both depressive and anxiety symptoms, i.e. up to two-thirds of all patients presenting with depressive symptoms have prominent anxiety symptoms.

Similar neuro-endocrine findings also occur in anxiety and depressive disorders. In addition, a number of family studies indicate that anxiety and depressive symptoms are genetically linked in at least some families. The use of particularly serotonergic drugs, e.g. selective serotonin re-uptake inhibitors (SSRIs), in treating both depressive and anxiety disorders has added to this (although higher doses tend to be more effective for treating the latter).

NEUROBIOLOGICAL RELATIONSHIPS

In both depressive and anxiety disorders (particularly panic) common findings include blunted cortisol response to adrenocorticotropic hormone (ACTH), blunted growth hormone (GH) response to clonidine, and blunted thyroid-stimulating hormone (TSH) and prolactin responses to thyrotropin-releasing hormone (TRH). In addition, hyperactivity of the noradrenergic system tends to occur (Table I).

CO-MORBIDITY

Specific anxiety disorders are commonly co-morbid with other anxiety disorders (e.g. GAD) and some patients may only present when co-morbid depression occurs. Although lower than the risk with depression, there is still a significantly higher risk of suicide in the longer term (especially with panic disorder) across all the anxiety disorders. As with depression, co-morbid personality disorders are common and tend to worsen the prognosis, lengthen inpatient treatment and increase the chances of treatment resistance or non-compliance as well as chronicity (with longer and more frequent stays in hospital) (Table II).

TREATMENT

In terms of pharmacological treatments, the overlap between effective treatments for anxiety disorders and depression is increasing, particularly with the advent of SSRIs. The effectiveness of the latter at lower dosages (20 mg equivalent of fluoxetine) for depression, or higher dose equivalents for other anxiety disorders (highest doses effective and required for OCD), have transformed treatment. Effectiveness of monoamine oxidase inhibitors (MAOIs) (e.g. tranylcypromine, phenelzine), reversible

Table I. **Neurobiology of general anxiety disorders**

	Neuroanatomy	Neurochemistry (neurophysiology)	Neuroimaging
Anxiety disorders in general	Amygdala — stress response, fear ± anxiety Cortical areas — cognitive misappraisal, fear Locus caeruleus — anxiety	↑CRF Abnormal NA system regulation & GABA & serotonin ± dopamine ↓Cortisol response to ACTH ↓GH response to clonidine ↓TSH & prolactin response to TRH Hyperactive NA function	↑Septohippocampal activity = anxiogenic Occasional cerebral ventricles (proportional to length of benzodiazepine exposure) increase in size
Major depressive disorder	Limbic system Basal ganglia Hypothalamus Medial thalamus Frontal lobe	↓Cortisol response to ACTH ↑Plasma corticol with DST non-suppression in 50% Abnormal NA system regulation + serotonin, GABA ± dopamine ↓GH response to clonidine ↓TSH + PRL response to TRH in 1/3 Antidepressants downregulate beta adrenoreceptors, $5HT_{1+2}$ receptor + increase GABA-B receptors	Ventricular enlargement (bipolar > unipolar), esp. with psychosis MRI→↓caudate nuclei ↑Deep white matter lesions in bipolars ↓Frontal blood flow

ACTH = adrenocorticotropic hormone; CFR = corticotropin-releasing factor; GABA = gamma-aminobutyric acid; GH = growth hormone; NA = noradrenergic; TSH = thyroid-stimulating hormone; TRH = thyrotropin-releasing hormone.

Table II. **Relationship between co-morbidities**

Anxiety disorder	With co-morbid MDD prevalent
Panic disorder ± agoraphobia	10 - 15% (33% and 67% before and after onset of panic disorder, respectively)
Social phobia	Common
Simple phobia	50 - 80%
OCD	67% (lifetime); 33% (current)
PTSD	Common — associated with severity and chronicity
GAD	Common

MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder.

MAOIs (moclobemide) or specific tricyclic agents (e.g. clomipramine 150 - 300 mg for OCD, imipramine 150 - 250 mg for panic disorder specifically) in anxiety with equivalent dose effectiveness for depressive disorders follows suit. Empirically, lower doses of SSRIs tend to be effective for depressive rather than anxiety disorders.

The use of beta-adrenergic blockers, e.g. propranolol, for symptomatic treatment of somatic anxiety symptoms such as palpitations and tremulousness is in contrast to the occasional potential for beta-blockers to cause depression or aggravate it in some circumstances. Serotonin$_{1A}$ (5-HT$_{IA}$) receptor agonists, e.g. buspirone or pindolol, have both anxiolytic and antidepressive augmenting effects.The use of agents such as venlafaxine, which at higher doses inhibits re-uptake of noradrenaline and serotonin, in treating depression as well as generalised anxiety and other anxiety disorders is also well established.

The selective responsiveness of anxiety disorders to cognitive-behavioural psychotherapy (CBT) (including specific phobias) using exposure, response prevention, desensitisation and psychoeducation is equivalent in outcome to pharmacotherapy. There are also additional benefits of reduced relapse after completion of therapy compared with stopping or weaning of pharmacotherapy, and side-effects are absent. This similarly applies to mild to moderate major depression in which the results for pharmacotherapy and CBT are equivalent. However, pharmacotherapy or electroconvulsive therapy (ECT) are the treatments of choice for major depression with psychosis.

References available on request.

IN A NUTSHELL

Depression and anxiety commonly occur together as symptoms or syndromes.

The lifetime prevalence of any anxiety disorder is 1 in 4 and of major depressive disorder 1 in 6.

Anxiety and depression may selectively distort cognitions and perceptions to fit the particular affect.

Common medical causes for anxiety and depression include hypoxia, epilepsy, amphetamines/cocaine/alcohol.

The amygdala mediates stress and fear responses, with the locus coeruleus/raphe nuclei mediating anxiety. Limbic system, basal ganglia and hypothalamic dysfunction occurs across the anxiety and depressive disorders.

In anxiety and depressive disorders, there is blunted cortisol response to ACTH, blunted GH response to clonidine, blunted TSH and prolactin responses to TRH, and noradrenergic system hyperactivity.

In general, MDD is co-morbid with all anxiety disorders.

Antidepressants (especially SSRIs) are also effective anxiolytics at higher doses.

CBT is effective in mild to moderate major depression and in most anxiety disorders, and produces less relapse on cessation compared with pharmacotherapy.