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Can We Distinguish Anxiety From Depression?

By David S. Baldwin, FRCPsych, Dwight L. Evans, MD, Robert M. A. Hirschfeld, MD, and Siegfried Kasper, MD

ABSTRACT ~ It is becoming increasingly apparent that although anxiety and depression are separate syndromes and can be identified as such, there is considerable overlap of clinical symptoms and pathophysiological processes. Data indicate that comorbid anxiety and depression is more common than either disorder alone. A large US study found that 58% of individuals with a history of depression also had an anxiety disorder, and a study by the World Health Organization showed that anxiety and depression were the most common coexisting psychological problems in primary care. Generalized anxiety disorder in particular is strongly comorbid with, and commonly precedes, major depression. The implications of comorbid anxiety and depression are significant, with increased social and psychological impairment, and poorer clinical outcomes and prognosis. Anxiety and depression coexist at much higher rates than would be expected by chance alone, suggesting that the two disorders are closely related and may have a common cause. Disturbances of serotonin and norepinephrine neurotransmission are both implicated in anxiety and depression, and new evidence suggests that these systems may provide a mechanistic link between the two disorders, with changes in one system being reflected in the other. Abnormal homeostasis of these two systems may result in anxiety and depression. New theories hypothesize a continuum of illness, with anxiety and depression possibly being different phenotypic expressions of a common neurobiological origin. There is still uncertainty regarding the neurobiological cause, but it is probably linked to dysregulation in the serotonergic and noradrenergic systems. *Psychopharmacology Bulletin*. 2002;36(Suppl 2):158-165

INTRODUCTION

Traditionally, anxiety and depression have been considered two distinct conditions and have been treated with either anxiolytics or antidepressants, respectively. However, it has become increasingly apparent that anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder, obsessive-compulsive disorder, specific phobia, and social anxiety disorder, share common symptoms with depression and

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frequently coexist. Approximately 60% of patients with depression have some symptoms of anxiety.¹ Data from the US National Comorbidity Survey indicate that patients with depression may experience, for example, comorbid social phobia (27%), simple phobia (24%), PTSD (19.5%), GAD (17%), and panic disorder (10%).² Similarly, many patients with an anxiety disorder also exhibit symptoms of depression.¹ Indeed, comorbidity of depression and anxiety is considered to be the rule rather than the exception.^{3,4} Analysis of odds ratios associated with lifetime and 12-month comorbidity indicates that major depression is most strongly comorbid with GAD, compared with other anxiety disorders.² As there are many overlapping symptoms of GAD and depression, treatment of these disorders may provide a diagnostic challenge to physicians.

The comorbidity of GAD and depression suggests either that one disorder is secondary to the other, or that there is a common cause which manifests in different ways.⁵ There is growing evidence that anxiety and depression may be different expressions of the same underlying neurobiological disorder. Data indicate that the balance of serotonin and norepinephrine is critical in the development of either GAD or depression. Research is now focused on trying to establish the mechanistic links between the serotonergic and noradrenergic systems, and to determine how each of these systems may influence the other.

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COMORBIDITY OF ANXIETY AND DEPRESSION

Evidence

There is increasing evidence^{2,6-8} indicating that many patients have symptoms of several psychiatric disorders, either simultaneously or in succession. In 1988, the World Health Organization launched a study to investigate psychological problems in primary care.⁹ Fifteen centers participated in the study, which were located throughout the world, to enable assessment in different cultures. At each center, 1,500 consecutive adult primary care attendees were screened using a range of questionnaires designed to assess general health status and disability. Patients also had their psychological status assessed by a primary care physician (PCP).

On average, one fourth of the patients in the study had a mental disorder, defined according to standard diagnostic criteria (*International Classification of Diseases, Tenth Revision [ICD-10]*). The most prevalent disorders were depression (10.4%), followed by generalized anxiety (7.9%). Interestingly, nearly half of the patients classified with an anxiety or depressive disorder were not recognized as having such a disorder by the PCP.

Almost half of the diagnosed "cases" of anxiety and depression occurred in the same patient and at the same time. Furthermore, the 9% of patients in the study who were "subthreshold" cases (ie, cases just missing the

severity threshold for anxiety and depression) showed high levels of overlap between the two disorders (Figure 1). Symptoms of anxiety and depression usually occurred together and in similar numbers (ie, patients diagnosed with depression also had similar numbers of anxiety symptoms).

The comorbid nature of anxiety and depression is confirmed by the US National Comorbidity Survey—a large-scale study in the general population.² This study used a modified version of the Composite International Diagnostic Interview (CIDI)¹⁰ to classify psychiatric disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised. (*DSM-III-R*).¹¹ Interviews with 8,098 patients, 15–54 years of age, from the general noninstitutionalized civilian population, revealed that major depressive disorder (MDD) had a high prevalence in the general population of the US, with a lifetime prevalence of 14.9%. Of those patients with a lifetime history of MDD, the majority (61.8%) were classified as having “secondary” MDD, as they had at least one other preexisting mental disorder (Figure 2). Significantly fewer patients (26%) had “pure” MDD, where MDD was their only reported lifetime mental disorder, and just 12.2% of patients had “primary” MDD. There were statistically significant gender differences within the population, indicating that MDD was more likely to be secondary in men than women ($P < .05$) and more likely to be “pure” in women than men ($P < .05$).

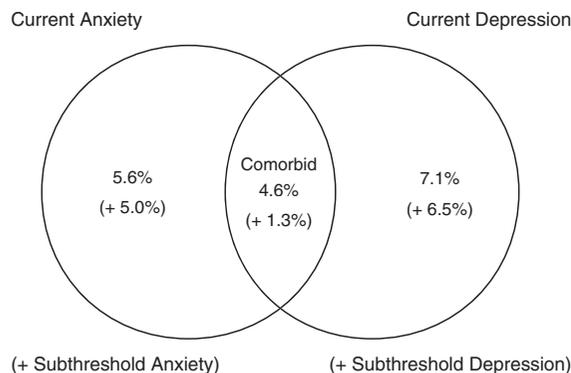
The survey reported that 58% of respondents with a lifetime history of depression also had an anxiety disorder, and 17.2% had GAD. In cases of secondary depression, anxiety disorders were the most common primary disorder (67.9%). Furthermore, primary anxiety disorders

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FIGURE 1

COMORBID DEPRESSION AND ANXIETY IN PRIMARY CARE



Adapted from: Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. *Br J Psychiatry*. 1990;168(suppl 30):38-43. Reprinted with permission from the Royal College of Psychiatrists.

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predicted the greatest risk of developing secondary depression, compared with other conditions.

There is extensive evidence showing that comorbidity of anxiety and depression is the rule rather than the exception. Depression occurring alone is rather uncommon, and the majority of major depressive episodes are associated with either current or previous comorbidity.

Consequences

Patients with comorbid anxiety and depression tend to suffer greater impairment than patients with either condition alone.⁶ The US National Comorbidity Survey found that patients with a primary anxiety disorder and secondary depression had significantly increased odds of a persistent illness ($P < .05$), in comparison to those with other primary diagnoses.² Comorbid anxiety and depression was also associated with a significantly greater social and occupational impairment, compared with either disorder alone.⁶ As a result of the increased severity and poorer prognosis of comorbid anxiety and depression, patients were more likely to seek medical assistance and receive medication.

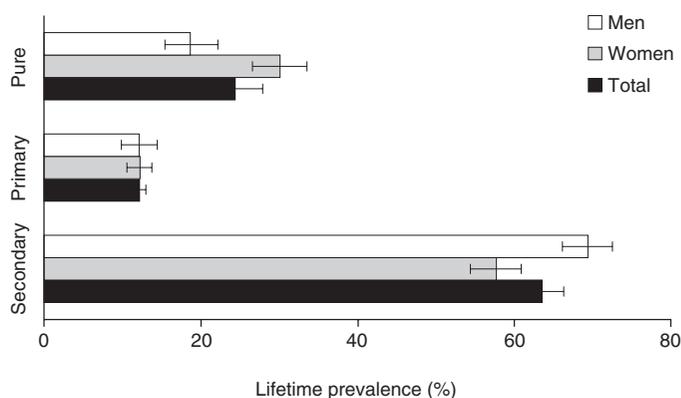
There may also be an increased risk of suicide attempts in patients with comorbid anxiety and depression, compared with those suffering from either disorder alone. The lifetime risk of suicide attempts for "pure" major depression or "pure" panic is similar (7.9% and 7%, respectively), but the risk

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FIGURE 2

LIFETIME PREVALENCE OF PURE, PRIMARY, AND SECONDARY MDD (\pm SE) IN THE US NATIONAL COMORBIDITY SURVEY



MDD=major depressive disorder.

Adapted from: Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of *DSM-III-R* major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry*. 1996;168(suppl 30):17-30.

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almost triples when anxiety and depression are comorbid (19.5%).¹² Other studies confirm the increased risk of attempted suicide associated with comorbid anxiety and depression. For example, a study of suicide attempts in adolescents with anxiety disorders showed that, of the 24 patients who attempted suicide, 21 (95%) had comorbid depression.¹³ In anxious patients who did not attempt suicide, only 5 (24%) had comorbid depression.¹³

Differences Between Anxiety and Depression

Although there is overlap of symptoms and strong links between anxiety and depression, plus a high level of coexistence, these disorders can be identified as separate conditions. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)¹⁴ has considerably refined the criteria for GAD.

Depressive disorders are distinguished from anxiety by the presence of features such as feelings of hopelessness, apathy, emotional withdrawal, and loss of interest or pleasure.¹⁵ By contrast, anxiety disorders are characterized by hypervigilance, agoraphobia, and compulsive traits (Figure 3).

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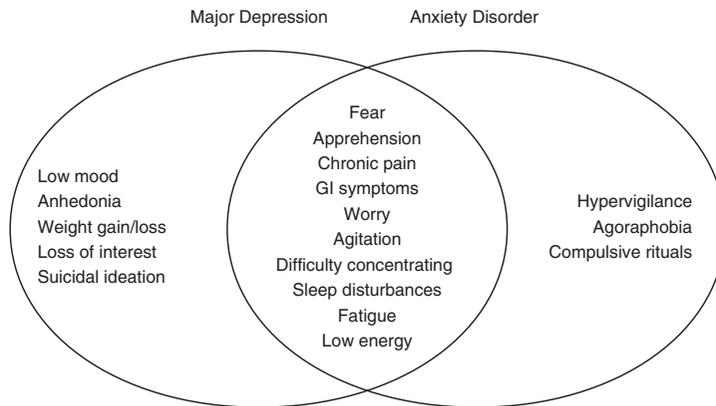
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PATHOPHYSIOLOGIC LINKS BETWEEN GAD AND DEPRESSION

Anxiety and depression coexist at higher rates than would be expected by chance, suggesting that the two conditions are closely linked and may have a common underlying cause. The exact causes are complex and not fully understood, although there is abundant evidence indicating that the norepinephrine (NE) and serotonin (5-HT) neurotransmitter systems are implicated in the pathophysiology of both disorders.¹⁶ Most data suggest

FIGURE 3

SYMPTOM OVERLAP BETWEEN ANXIETY AND DEPRESSION



GI=gastrointestinal.

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that anxiety and depression are associated with increased NE transmission and reduced 5-HT transmission,¹⁶ but this concept is controversial and probably oversimplified.

Elevated levels of NE in the periphery are associated with somatic manifestations of anxiety such as increased pulse rate, increased blood pressure, dry mouth, and cessation of intestinal peristalsis.¹⁷ Drugs (eg, yohimbine) that increase firing of noradrenergic neurons located in the locus coeruleus induce symptoms of anxiety in humans, whereas drugs that reduce noradrenergic firing (eg, clonidine) inhibit these symptoms.¹⁸

Studies have implicated 5-HT in certain components of anxiety and depression, particularly alterations in appetite, energy, sleep, mood, libido, and cognitive function.¹⁹ In addition, many investigations have shown that decreased levels of 5-HT are associated with depression.²⁰ Selective serotonin reuptake inhibitors have been shown to be effective in the treatment of anxiety and depression, and are now often regarded as the first-line treatment for anxiety disorders.²¹ Venlafaxine extended release, a serotonin and norepinephrine reuptake inhibitor, is also effective in the treatment of anxiety and depression.

It has been suggested that the "balance" of 5-HT and NE, rather than the "absolute" levels of each neurotransmitter affects anxiety and depression.²² In other words, these disorders are associated with abnormalities in the regulation of these neurotransmitters. The 5-HT and NE systems are so closely linked that changes in one are reflected in the other.⁴ Indeed, it has been shown that the raphe nuclei (body of serotonergic neurons) and locus coeruleus are interconnected and mutually inhibitory.²³

New hypotheses propose a continuum of illness, with anxiety and depression possibly being different phenotypic expressions sharing a common neurochemical origin.^{22,24} The common neurochemical origin probably involves the 5-HT and NE systems, although dysfunction in these systems is not likely to be the primary pathophysiological alteration in anxiety and depression.¹⁶ It is more likely that 5-HT and NE are implicated in anxiety and depression due to their role in modulating, and being modulated by, other neurobiological systems.¹⁶ It is proposed that NE dysfunction initiates a cascade of events that begins with states of anxiety and gradually evolves into depressive states.²⁵ Alternatively, 5-HT dysregulation may predispose to NE hyperactivity, resulting in increased depressive symptoms. Furthermore, a common genetic basis to GAD and MDD has been shown, but the development of either disorder is dependent on environmental factors.²⁶

CONCLUSION

Although anxiety and depression may be separate entities, the two disorders show considerable overlap of clinical symptoms, and possibly have

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similar pathophysiological processes. Indeed, anxiety and depression often coexist and several studies have shown that comorbid anxiety and depression is more common than either condition alone. The consequences of comorbid anxiety and depression are significantly different from those of either disorder alone, with patients having a reduced response to treatments, worse prognosis, and increased social and psychological impairment.

The overlapping symptomatology of anxiety and depression can make it difficult to diagnose the individual disorders. However, there are certain characteristics that are unique to each and these can be useful aids to the physician when considering the most appropriate treatments.

The comorbidity of anxiety and depression suggests a common cause and there is increasing evidence that the two disorders are different expressions of the same underlying neurobiological disorder. The interplay and homeostasis of the 5-HT and NE systems may provide a mechanistic link between anxiety and depression, although the primary cause of the dysregulation in the neurotransmitter systems remains unclear. ❖

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DISCLOSURE

Dr. Baldwin is on the advisory board of Wyeth.

REFERENCES

1. Keller MB, Hanks DL. Anxiety symptom relief in depression treatment outcomes. *J Clin Psychiatry*. 1995;56(suppl 6):22-29.
2. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of *DSM-III-R* major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry*. 1996;168(suppl 30):17-30.
3. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. *J Clin Psychiatry*. 1999;60(suppl 22):29-34.
4. Ninan PT. The functional anatomy, neurochemistry, and pharmacology of anxiety. *J Clin Psychiatry*. 1990;60(suppl 22):12-17.
5. Kasper S. Depression and anxiety— separate or continuum? *World J Biol Psychiatry*. 2001;2:162-163.
6. Kessler RC, DuPont RL, Berglund P, Wittchen HU. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. *Am J Psychiatry*. 1999;156:1915-1923.
7. Sanderson WC, Barlow DH. A description of patients diagnosed with *DSM-III-R* generalized anxiety disorder. *J Nerv Ment Dis*. 1990;178:588-591.
8. Wittchen HU, Zhao S, Kessler RC, Eaton WW. *DSM-III-R* generalized anxiety disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51:355-364.
9. Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. *Br J Psychiatry*. 1990;168(suppl 30):38-43.
10. World Health Organization. *Composite International Diagnostic Interview (CIDI)*. Version 1. Geneva, Switzerland: World Health Organization; 1990.
11. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed rev. Washington, DC: American Psychiatric Association; 1987.
12. Johnson J, Weissman MM, Klerman GL. Panic disorder, comorbidity, and suicide attempts. *Arch Gen Psychiatry*. 1990;47:805-808.
13. Pawlak C, Pascual-Sanchez T, Raë P, Fischer W, Ladame F. Anxiety disorders, comorbidity, and suicide attempts in adolescence: a preliminary investigation. *Eur Psychiatry*. 1999;14:132-136.

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14. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
15. Kuzel RJ. Treating comorbid depression and anxiety. *J Fam Pract*. 1996;43(suppl 6):S45-S53.
16. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress Anxiety*. 2000;12(suppl 1):2-19.
17. Birkmayer W, Reiderer P. *Understanding the Neurotransmitters: Keys to the Workings of the Brain*. New York, NY: Springer-Verlag Wein; 1989.
18. Grimsley SR. Anxiety disorders. In: Young LY, Koda-Kimble MA, eds. *Applied Therapeutics: the Clinical Use of Drugs*. 6th ed. Vancouver, British Columbia: Applied Therapeutics Inc.; 1995:1-31.
19. Laird LK, Benfield WH. Mood disorders I: major depressive disorders. In: Young LY, Koda-Kimble MA, eds. *Applied Therapeutics: the Clinical Use of Drugs*. 6th ed. Vancouver, British Columbia: Applied Therapeutics Inc.; 1995:1-28.
20. Delgado PL, Price LH, Heninger GR, Charney DS. Neurochemistry. In: Paykel E, ed. *Handbook of Affective Disorders*. 2nd ed. New York, NY: Guilford Press; 1992:219-253.
21. Pollack MH, Marzol PC. Pharmacotherapeutic options in the treatment of comorbid depression and anxiety. *CNS Spectrums*. 2000;5:23-30.
22. Casacalenda N, Boulenger JP. Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications. *Can J Psychiatry*. 1998;43:722-730.
23. Mongeau R, Blier P, de Montigny C. The serotonergic and noradrenergic systems of the hippocampus: their interaction and the effects of antidepressant treatment. *Brain Res Rev*. 1997;23:145-195.
24. Gorman JM. Comorbid depression and anxiety spectrum disorders. *Depress Anxiety*. 1996;4:160-168.
25. Paul SM. Anxiety and depression: a common neurobiological substrate?. *J Clin Psychiatry*. 1988;49(suppl):13-16.
26. Kendler KS. Major depression and generalized anxiety disorder. Same genes, (partly) different environments—revisited. *Br J Psychiatry*. 1996;168(suppl 30):68-75.

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