The Impact of Comorbidity on the Treatment of Panic Disorder

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Panic disorder comorbid with other psychiatric conditions appears to be more common than panic disorder alone. Depression is the most frequently associated disorder. This article reviews the detrimental effects of comorbidity on the severity and course of panic disorder. The presence of comorbidity results in more severe anxiety and depressive symptoms, a higher rate of suicide attempts, a higher frequency of other comorbid conditions, and a poorer response and compliance to treatment. Thus, it is important for physicians to be aware of the possibility of comorbidity in patients with panic disorder in order to select the most appropriate therapy to target all components of their condition.

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Comorbidity of psychiatric disorders is common. The National Comorbidity Survey,[1] a nationwide survey of the U.S. general population, found that the majority of lifetime disorders (79%) were comorbid disorders. Panic disorder comorbid with depression is more the rule than the exception: around two thirds of patients with panic disorder have experienced a major depressive disorder at some time.[2,3] Panic disorder can also be comorbid with other psychiatric conditions such as social phobia, obsessive-compulsive disorder, alcohol abuse, or personality disorders.

This review assesses the prevalence of comorbid panic and depressive disorders in primary care and the consequences of comorbidity on the course of the illness and the response to treatment.

COMORBID PANIC AND DEPRESSION IN PRIMARY CARE

The World Health Organization (WHO) Collaborative Study on Psychological Problems in General Health Care[4,5] explored the form, frequency, course, and outcome of mental disorders (according to ICD-10 criteria) among primary health care patients in 14 countries. The study found that psychiatric comorbidity was common, with 9.5% of patients being affected by 2 or more disorders.[6] The overlap between anxiety disorders and depressive disorders was particularly great.[7] Of those with a current anxiety disorder, about 45% also had a current depressive disorder, and about 40% of those with a current depressive disorder had a current anxiety disorder (Figure 1). Table 1 shows the odds ratios for comorbidity between psychiatric disorders. The association between depression and anxiety disorder, including panic disorder, was stronger than that between the anxiety disorders themselves (with the exception of panic disorder and agoraphobia). For example, depressed patients were 12 times more likely to present with comorbid panic disorder than should occur by chance, compared with patients with generalized anxiety disorder who were 7 times more likely to present with comorbid panic disorder.

A high comorbidity with psychiatric disorders was also found among patients with current or lifetime panic attacks, rather than a diagnosis of panic disorder.[7] From a total of 227 patients, 138 had a diagnosis of panic disorder with or without agoraphobia, 61 had a diagnosis of another disorder (for example, depression or generalized anxiety disorder), and 26 had subthreshold psychiatric symptoms. Only 2 patients were not suffering from a psychiatric disorder or subthreshold symptoms. Thus, the presence of panic attacks is a strong indicator that the existence of psychiatric disorders should be investigated in these patients. This holds true for patients with a history of panic attacks as well as current experience of panic attacks.

Figure 2 shows the incidence of current ICD-10 disorders in patients with lifetime signs of panic attacks. Unexpectedly, more patients with lifetime signs of panic currently reached diagnostic criteria for depression (45.6%) than for panic disorder (42.6%).[7] Thus, it appears that the existence of panic attacks predicts the development of depression at least as much as it predicts panic disorder or other psychiatric disorders.

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Figure 1. Comorbidity of Depressive and Anxiety Disorders in Current, Well-Defined Cases From the World Health Organization Collaborative Study on Psychological Problems in General Health Care

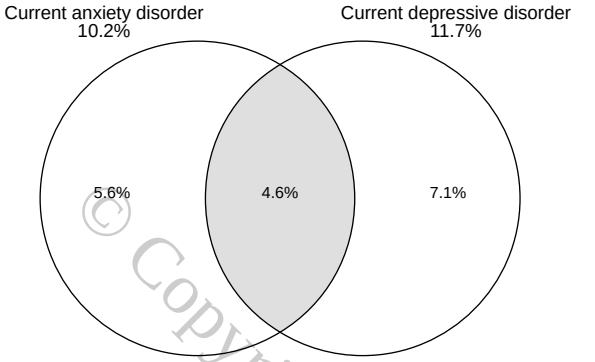
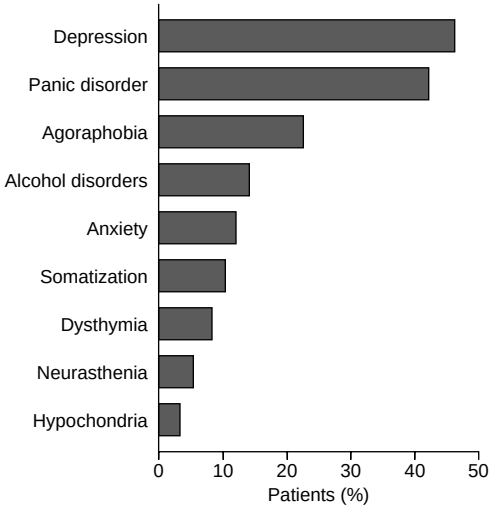


Table 1. Current Comorbidity Between ICD-10 Diagnoses Measured by Odds Ratios on Weighted Numbers*

	Depressive Episode	Dysthymia	Generalized Anxiety Disorder	Agoraphobia, With or Without Panic
Dysthymia	6.6			
Generalized anxiety disorder	10.3	9.9		
Agoraphobia, with or without panic	8.8	6.0	5.6	
Panic disorder	12.2	7.7	6.9	45.4

*From the World Health Organization Collaborative Study on Psychological Problems in General Health Care, reference 7.

Figure 2. Frequency of ICD-10 Disorders in Patients With Lifetime Signs of Panic Attacks From the World Health Organization Collaborative Study on Psychological Problems in General Health Care



The consequences of comorbidity on the patients' mental health were assessed in the WHO Collaborative Study using the 28-item General Health Questionnaire (GHQ-28).[7] Patients with no disorder had a low mean GHQ-28 score of 3 points, while patients with panic disorder or depression scored 7 points and 12 points, respectively. In comparison, patients suffering from comorbid depression and panic disorder had a mean GHQ-28 score of 17 points, indicating a greater severity of mental illness in comorbid patients than in those suffering from a single disorder. This is reflected in the incidence of suicide attempts. Among patients with comorbid panic disorder and depression, 43% had a history of suicide attempts, compared with 17% of those with depression alone.

EFFECTS OF COMORBIDITY ON THE OUTCOME OF PANIC DISORDER

Follow-up studies of up to 20 years in duration have demonstrated the poor long-term outcome of panic disorder.[8] Less than half of all patients become panic-free even after many years of treatment, while only one third become free of agoraphobia or depression. A mere 10% of patients achieve panic-free status with no depressive symptoms and no role impairment. Given that the treatment of panic disorder alone can have a poor outcome, what are the consequences of concurrent depression on treatment outcome?

Effect of Comorbidity on Response to Treatment

The presence of comorbid depression has a variable effect on the response to treatment of panic disorder, with some studies showing no effect and others showing a detrimental effect on treatment outcome.

In studies by Black et al.,[9] Keller et al.,[10] and Lesser et al.,[11] the response to treatment with fluvoxamine, alprazolam, or imipramine was not affected by the presence of comorbid depression, even though comorbid patients were more likely to have severe phobic avoidance, anxiety, and disability. Maddock et al.[12] found that a history of major depression had no effect on the outcome of treatment with adinazolam in patients with panic disorder. However, a small number of patients with a history of recurrent major depression exhibited a poorer response to treatment than patients with no history of depression. Conversely, in an 8-week placebo-controlled study[13] of alprazolam in panic disorder, overall improvement was weakly predicted by more severe depression at baseline. The investigators suggest that when depressive symptoms respond to treatment, the patient experiences a greater sense of improvement than that experienced in the absence of depressive symptoms.

The majority of studies, however, show that treatment response in patients with comorbid panic and depression is poorer than in patients with panic disorder alone. Van

Valkenburg et al.[14] studied 114 patients from inpatient and outpatient psychiatric clinics. Treatment response was considered to be poor when the practitioners had exhausted all treatments or the patient had discontinued treatment without showing clinical improvement. In a significantly higher proportion of patients suffering from depression with secondary comorbid panic disorder, the treatment response was poor (55%) compared with patients with panic disorder alone (28%, $p < .01$).

Scheibe and Albus[15] conducted a 2-year follow-up study of 52 patients with panic disorder who presented at an outpatient unit for anxiety disorders. At intake, patients with comorbid depression had more severe symptoms of depression and anxiety and more severe impairment in work and family life activities than patients without depression. After 2 years of naturalistic treatment, the patients with comorbid depression at intake still showed more severe phobic symptoms and impairment in work and family life than patients with panic disorder alone. At the 2-year follow-up, 75% of the patients with panic disorder alone at intake were in remission (i.e., did not meet DSM-III-R criteria for anxiety or depressive disorders), compared with 35% of the comorbid patients. Symptoms persisted throughout treatment in nearly half of the comorbid patients, compared with 9% of the patients with panic disorder alone. At a subsequent 5-year follow-up, the comorbid group was still experiencing more severe symptoms of anxiety and depression and poorer psychosocial functioning than the group with panic disorder alone.[16] The investigators also found that the presence of agoraphobic avoidance at intake was a predictor for a poor treatment outcome.

Interestingly, the poor response to treatment seen in patients with comorbid panic and depression also seems to occur with placebo treatment. In a study by Coryell and Noyes,[17] 43 patients with panic disorder received placebo, and 25% showed a marked improvement after 8 weeks. Patients without a placebo response were roughly twice as likely to have been suffering from comorbid major depression at the beginning of the study.

Even when comorbid depression is not present at initial presentation, patients with panic disorder often develop depression. In a 6-year naturalistic follow-up study[18] of 55 patients with panic disorder, 18% developed major depression. In addition, 11% were suicidal, 14% had developed alcoholism, 26% still suffered from panic attacks, and 37% were agoraphobic. Thus, it is important that practitioners remain alert to the possibility of comorbid depression throughout the patient's treatment plan, given the detrimental effect comorbidity has on treatment outcome.

Effect of Comorbidity on Treatment Compliance

Comorbidity may affect compliance as well as the response to the treatment. In a primary care study involving depressed patients with or without a comorbid lifetime anxiety disorder, Brown and colleagues[19,20] found they could distinguish between depressed patients with a history of panic disorder, depressed patients with generalized anxiety disorder, and patients with depression alone by the presence of certain factors. The patients with comorbid panic disorder were more likely to present with greater depressive severity and greater impairment in physical and psychosocial functioning, and were more likely to have a history of alcohol dependence, somatization disorder, and avoidant personality disorder. Furthermore, depressed patients with lifetime panic disorder were more likely to terminate both pharmacotherapy and psychotherapy prematurely during the acute phase of treatment (Table 2). These results highlight the importance of selecting an appropriate treatment for patients with comorbid panic disorder. More patients in the comorbid depression and panic group discontinued acute treatment with nortriptyline treatment than in the depression alone or comorbid depression and generalized anxiety groups, suggesting that poor tolerability of the medication was an issue. Thus, selecting an antidepressant with a more favorable side effect profile, such as a serotonin selective reuptake inhibitor (SSRI), is important to avoid arousing physical sensations of panic.

Table 2. Dropout Rates for Depressed Primary Care Patients Randomly Assigned to Treatment With Nortriptyline or Interpersonal Psychotherapy*

	Major Depression		
Dropout (%)	Alone	+ Generalized Anxiety Disorder	+ Panic Disorder
Nortriptyline			
Acute (2 mo)	29	32	48
Continuation (6 mo)	40	47	29
Psychotherapy			
Acute (6 mo)	31	40	53
Continuation (2 mo)	20	8	20

*Data from references 19 and 20.

CONCLUSIONS

Comorbid depression is frequently seen in patients with panic disorder. The presence of comorbidity results in more severe anxiety and depressive symptoms, a higher rate of suicide attempts, a higher frequency of other comorbid conditions such as alcoholism, a poorer response, and poorer compliance with treatment than in patients with panic disorder or depression alone.

Effective treatment of panic disorder clearly involves the recognition and appropriate treatment of the comorbid condition. Only when both disorders are adequately treated can the patients regain their normal level of functioning and enhance their quality of life.

Drug names: adinazolam mesylate (Deracyn), alprazolam (Xanax), fluvoxamine (Luvox), imipramine (Tofranil and others), nortriptyline (Pamelor and others).

REFERENCES

1. Kessler RC, McGonale 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. Cowley DS, Flick SN, Roy-Byrne PP. Long-term course and outcome in panic disorder: a naturalistic follow-up study. Anxiety 1996;2:13–21
3. Stein MB, Tancer ME, Uhde TW. Major depression in patients with panic disorder: factors associated with course and recurrence. J Affect Disord 1990;19:287–296
4. Sartorius N, Üstün TB, Costa e Silva JA, et al. An international study of psychological problems in primary care: preliminary report from the World Health Organization collaborative project on "Psychological Problems in General Health Care." Arch Gen Psychiatry 1993;50:819–824
5. Von Korff M, Üstün TB. Methods of the WHO Collaborative Study on "Psychological Problems in General Health Care." In: Üstün TB, Sartorius N, eds. Mental Illness in General Health Care: An International Study. New York, NY: John Wiley & Sons; 1995:19–36
6. Goldberg DP, Lecrubier Y. Form and frequency of mental disorders across centres. In: Üstün TB, Sartorius N, eds. Mental Illness in General Health Care: An International Study. New York, NY: John Wiley & Sons; 1995: 323–334
7. Lecrubier Y, Üstün TB. Panic and depression: a worldwide primary care perspective. Int Clin Psychopharmacol 1998;13(suppl 4):7–11
8. Keller MB, Baker LA. The clinical course of panic disorder and depression. J Clin Psychiatry 1992;53(3, suppl):5–8
9. Black DW, Wesner R, Bowers W, et al. Acute treatment response in outpatients with panic disorder: high versus low depressive symptoms. Ann Clin Psychiatry 1995;7:181–188
10. Keller MB, Lavori PW, Goldenberg IM, et al. Influence of depression on the treatment of panic disorder with imipramine, alprazolam and placebo. J Affect Disord 1993;28:27–38
11. Lesser IM, Rubin RT, Pecknold JC, et al. Secondary depression in panic disorder and agoraphobia, I: frequency, severity, and response to treatment. Arch Gen Psychiatry 1988;45:437–443
12. Maddock RJ, Carter CS, Blacker KH, et al. Relationship of past depressive episodes to symptom severity and treatment response in panic disorder with agoraphobia. J Clin Psychiatry 1993;54:88–95
13. Woodman CL, Noyes R Jr, Ballenger JC, et al. Predictors of response to alprazolam and placebo in patients with panic disorder. J Affect Disord 1994;30:5–13
14. Van Valkenburg C, Akiskal HS, Puzantian V, et al. Anxious depressions: clinical, family history, and naturalistic outcome: comparisons with panic and major depressive disorders. J Affect Disord 1984;6:67–82
15. Scheibe G, Albus M. Prospective follow-up study lasting 2 years in patients with panic disorder with and without depressive disorders. Eur Arch Psychiatry Clin Neurosci 1994;244:39–44
16. Scheibe G, Albus M. Predictors on outcome in panic disorder: a 5-year prospective follow-up study. J Affect Disord 1996;41:111–116
17. Coryell W, Noyes R. Placebo response in panic disorder. Am J Psychiatry 1988;145:1138–1140
18. Lepola U, Koponen H, Leinonen E. A naturalistic 6-year follow-up study of patients with panic disorder. Acta Psychiatr Scand 1996;93:181–183
19. Brown CB, Shulberg HC, Madonia MJ, et al. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996;153:1293–1300
20. Brown CB, Shulberg HC, Shear MK. Phenomenology and severity of major depression and comorbid lifetime anxiety disorders in primary medical care practice. Anxiety 1996;2:210–218