

## New Drug Class for Comorbid Depression

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### **Abstract**

The high prevalence of comorbid psychiatric disorders in patients with major depression can make diagnosis difficult and treatment complicated. Only recently have clinicians understood that depressed patients often will have a history of other psychiatric disorders or will present with concurrent symptoms of anxiety disorders, such as panic or obsessive-compulsive disorder. Patients with comorbid psychiatric disorders are more likely than those with only one condition to attempt suicide, require hospitalization, encounter more social and on-the-job problems, and have poorer short- and long-term prognoses. This review examines the prevalence of comorbid psychiatric disorders; the three theories about this comorbidity; the importance of pharmaceutical treatment; and the cost-effectiveness of a new class of antidepressants, the selective-serotonin reuptake inhibitors. This class of drugs was first approved for depression, for which their efficacy equaled that of other antidepressants. Recently, two SSRIs have been approved for obsessive-compulsive disorder, and research has shown that these agents also are effective in the treatment of panic disorder. Studies have suggested that the selective-serotonin reuptake inhibitors may be more cost-effective than older antidepressants because their favorable side-effect profiles may result in improved patient compliance. The wide efficacy and minimal side effects of these agents may make them a viable first-line treatment in patients with comorbid psychiatric disorders.

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**M**ore often than not, depressed patients will present with comorbid conditions, such as depression and panic disorder or depression and obsessive-compulsive disorder. Symptoms of de-

pression include low mood, lack of interest in normal activities, sadness, inactivity, inability to concentrate, feelings of despair and hopelessness, and, sometimes, suicidal urges. Panic disorder is recognized by distinct panic attacks in which the patient experiences such symptoms as heart palpitations, sweating, trembling, shortness of breath, choking, chest pain or discomfort, nausea, and a sense of losing control. Patients with obsessive-compulsive disorder experience obsessions (ie, recurrent ideas, impulses, or mental images that are irrational and disturbing) or compulsions (behaviors recognized as excessive but that still are performed repetitively).<sup>1</sup>

In many cases, the symptoms overlap. For example, depressed patients often show signs of anxiety and agitation; they may even experience short panic attacks, making it difficult to differentiate between the two disorders.<sup>2</sup>

Only recently has the wide prevalence of depression with comorbid anxiety or panic disorder become accepted, and three theories have emerged on the classification of these comorbid conditions. The first is that the two concurrent diseases represent discrete manifestations of the same disorder. The second states that the comorbid condition is a separate disorder, different from each of the diseases. According to the third, the comorbid condition indicates the presence of two distinct disorders in one patient. Regardless of which theory practitioners follow, the diagnosis of comorbid conditions is difficult, and their treatment requires a flexible approach.<sup>3</sup>

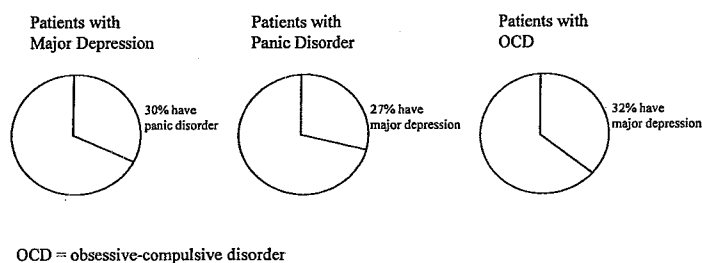
### **Comorbidity Figures**

Recent research suggests that this comorbidity of psychiatric disorders may be the norm, rather than the exception (Figure 1). According to a review by Lydiard, as many as 60% of patients diagnosed with major depression also have anxiety, and 20% to 30% meet diagnostic criteria for panic disorder.<sup>4</sup> Of those with diagnosed panic disorder, 27% have depression.<sup>5</sup> Moreover, about one third of patients with obsessive-

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**Figure 1.** Comorbidity of Depression, Panic Disorder, and Obsessive-Compulsive Disorder



Adapted from Zajecka and Ross, 1995,<sup>3</sup> Lydiard, 1991,<sup>4</sup> and Leon et al, 1995.<sup>5</sup>

compulsive disorder fulfill diagnostic criteria for major depression.<sup>3</sup>

The National Comorbidity Survey indicated that the prevalence of psychiatric disorders is higher than previously acknowledged.<sup>6</sup> This survey of 8,098 respondents found that about 50% had at least one such disorder over their lifetime, and that about one fourth had more than one (Table 1).

The older Epidemiologic Catchment Area study, which surveyed more than 18,500 people, found that 6% of men and 13% of women had suffered at least one anxiety disorder during the 6-month period preceding the interview.<sup>5</sup> According to Epidemiologic Catchment Area data, the lifetime prevalence rate of obsessive-compulsive disorder in North America is 2% to 3%;<sup>7</sup> however, this estimate may be low, because some cases remain undiagnosed.<sup>8</sup> The study also reported a 1.6% lifetime prevalence for panic disorder, which was present in about 2% of women and 1% of men.<sup>9</sup> Conversely, the National Comorbidity Survey reported a higher lifetime prevalence for panic disorder—3.5%. In that more recent study,

panic disorder was found in 5% of women and 2% of men.<sup>6</sup>

In the National Comorbidity Survey, anxiety disorders were more likely to occur in the 12 months preceding the interview (17%) than were mood disorders (11%) or substance abuse disorders (11%).<sup>6</sup> In addition, women were more likely than men to suffer a mood disorder, and to have higher rates of lifetime and 12-month comorbidity of three or more conditions. Among the groups surveyed, higher prevalences of psychiatric disorders

were found in the 25- to 34-year age group and in the lowest income and education groups.<sup>6</sup>

Data from the National Comorbidity Survey show that the vast majority of disorders in the sample were comorbid. In addition, respondents with three or more lifetime disorders accounted for the largest share of respondents with any disorder. For disorders that occurred during the 12 months preceding the interview, this group accounted for almost 60% of all disorders and almost 90% of severe disorders. Moreover, only about 40% of patients with a psychiatric disorder, including patients with severe comorbid conditions, sought professional help from a mental health specialist.<sup>6</sup>

This high rate of comorbidity indicates a critical need for accurate diagnosis, as patients with more than one mental disorder generally are more severely impaired than are those with only one. They require more frequent hospitalizations, suffer greater social and on-the-job difficulties, are more likely to attempt suicide, and have poorer short- and long-term prognoses.<sup>3</sup> Weismann and colleagues<sup>10</sup> examined the Epidemiologic Catchment Area population and found that patients with panic disorder had the greatest number of suicidal thoughts and attempts, followed, in order, by those who suffer panic attacks, have any other psychiatric disorder, and have no psychiatric disorder. Twenty percent of patients with panic disorder had attempted suicide at some point in their lives, compared with 12% of those with panic attacks, 6% with a different psychiatric disorder, and 1% who had no psychiatric disorder.

This comorbidity may be caused by the neurotransmitter serotonin. When serotonergic function is abnormal, symptoms can appear that indicate the presence of depression, panic, obsessive-compulsive disorder, or other psychiatric disorders.

**Table 1.** The Concentration of Lifetime and 12-Month Psychiatric Disorders Among Persons with Comorbidity

Number of Lifetime Psychiatric Disorders	Proportion of Sample (%)	Proportion with Severe 12-Month Disorders (%)
0	52.0	—
1	21.0	2.6
2	13.0	7.9
≥3	14.0	89.5

Data from Kessler et al, 1994.<sup>6</sup>

### Obsessive-Compulsive Disorder Hinges on Serotonergic Activity

Numerous chemical factors can contribute to the development of depression, but serotonin dysfunction appears to be the key in obsessive-compulsive disorder. Clinical trials with a number of tricyclic agents, monoamine oxidase (MAO) inhibitors, anxiolytics, and antipsychotic drugs have confirmed the critical role of serotonergic activity in obsessive-compulsive disorder.<sup>11</sup> Only one of these drugs, the tricyclic agent clomipramine, had any measurable efficacy, a result of its potent inhibition of serotonin reuptake. The selective-serotonin reuptake inhibitors (SSRIs) represent an improvement in obsessive-compulsive disorder therapy because they are more serotonin specific and cause fewer side effects than do older drugs.<sup>11</sup>

Although obsessive-compulsive disorder and depression may share the serotonin link, research suggests that obsessive-compulsive disorder is, in fact, a separate disorder.<sup>8</sup> Depression and obsessive-compulsive disorder often run in families, although a genetic link between the two has not been confirmed. Furthermore, the debate over whether depressive symptoms are integral to obsessive-compulsive disorder or whether they represent an unrelated, secondary disorder remains unresolved. Research indicates that symptoms of depression improve as the obsessive-compulsive disorder responds, although the conditions improve at different rates.<sup>8</sup> Symptoms of obsessive-compulsive disorder may improve as early as 1 week after initiation of drug therapy, whereas symptoms of depression may take 4 weeks or longer. Part of the explanation is the low placebo-response rate in obsessive-compulsive disorder (5%) compared with that in depression (30% to 50%).<sup>8</sup>

Obsessive-compulsive disorder is classified as an anxiety disorder, despite significant differences between obsessive-compulsive disorder and anxiety in prevalence, by gender; stability of diagnosis; and response to treatment. Diagnosis of obsessive-compulsive disorder depends on evidence that the patient has obsessional thoughts or performs compulsive behaviors. The condition differs from depression in that it is highly dependent on serotonergic causes and, thus far, responds only to serotonin-specific drug therapy, independent of concomitant depressive or anxiety syn-

dromes. However, the improvement of depressive and anxiety symptoms appears dependent on the response of the obsessional symptoms. Thus, many clinicians believe that treatment of obsessive-compulsive disorder should take priority when symptoms of major depression also are present.<sup>8</sup>

### Link Between Panic and Depression

Successful treatment of panic disorder also may depend on the outcome of the treatment of depressive symptoms. One study<sup>12</sup> showed that patients with panic generally progress to experiencing both panic and depression or depression alone.

In a population-based study of 12,668 people, those with both panic and depression had more severe symptoms than did those who had only one condition.<sup>13</sup> The study also reported that the symptom profiles of patients with single and comorbid conditions were similar, and that the more severe symptoms of depression, such as guilt and suicidal impulses and actions, were more frequent in patients with both depression and panic (Table 2).

Grunhaus and colleagues<sup>14</sup> reported that patients with comorbid panic disorder and depression developed symptoms, sought treatment, and required hospitalization at a younger age than did those with depression alone. Patients in the comorbid subgroup also had more severe symptoms and more frequent psychiatric hospital admissions for major depressive disorder than did those with depression alone. However, the study found no differences in psychosocial functioning between the two groups.

In patients with comorbid depression and panic disorder, a roughly even percentage of patients de-

**Table 2.** Symptoms of Depression in Patients with Depression Alone, Panic Attacks Alone, and Both Depression and Panic Attacks

Symptoms	Percentage Reporting Symptoms		
	Major Depression Only (n = 512)	Panic Attacks Only (n = 511)	Depression and Panic (Comorbid) (n = 262)
Dysphoria	100.0	62.5	100.0
Weight Problems	73.6	9.2	73.0
Sleep Problems	81.2	13.5	89.7
Motor Problems	45.5	4.3	59.5
Lack of Sexual Interest	34.6	3.0	37.0
Fatigue	60.0	7.2	66.4
Guilt	58.0	11.0	71.4
Slow Thoughts	75.6	8.6	77.5
Suicidal Thoughts or Attempts	72.5	15.3	84.8

Data from Andrade et al, 1994.<sup>13</sup>

velop depression first, panic first, or both conditions simultaneously. No conclusive evidence has been found to support the argument that a difference in outcomes is based on which condition presented first, and studies have supported both sides of the debate.<sup>4</sup>

According to a study on the costs and other effects of panic disorder, proper diagnosis can increase the cost-effectiveness of treatment of these patients, as a large component of the cost of treating panic disorder is related to misdiagnosis.<sup>15</sup> The researchers concluded that misdiagnosis leads to greater use of health services that are ineffective because they do not result in clinical improvement. Moreover, although mental health treatment costs may climb because expenditures for psychiatric care and pharmaceutical agents increase, overall costs will decline because of lower healthcare utilization, reduced absenteeism, and higher productivity. The study concluded that improved knowledge about panic disorder, particularly among primary care physicians, neurologists, and cardiologists, may contribute to overall cost reductions in caring for persons with the disorder.

#### Mixed Anxiety-Depression Disorder

Recent research points to evidence of a separate disorder, known as mixed anxiety-depression, in which patients' symptoms do not meet diagnostic criteria for either an anxiety or mood disorder. The condition affects as many as 10% of patients with depressive symptoms.<sup>4</sup> These patients represent less severe cases than do those with more debilitating symptoms, and they use fewer healthcare resources. However, like those with more severe cases, their symptoms may make it difficult for them to function in social and professional environments.

#### Efficacy of Serotonin-Specific Agents

Recent research has suggested that the SSRIs have a broad range of activity against several mental disorders whether occurring by themselves or concurrently.<sup>16,17</sup> The benefit of these agents has surfaced indirectly with the finding that certain older antidepressants with some activity in serotonin inhibition also were effective for the treatment of such conditions as panic disorder and obsessive-compulsive disorder. This breakthrough helped to clarify the complex interrelationships that made diagnosis and treatment of these mental disorders difficult.

This discovery was particularly important with respect to obsessive-compulsive disorder, about which little was known, because the disease is closely tied to serotonin function. It also enabled serotonin-specific agents, namely, the SSRIs, to become accepted

for the treatment of anxiety, panic disorder, obsessive-compulsive disorder, and other conditions, as well as for depression (their initial indication). The broad-spectrum efficacy of SSRIs in these related disorders gives physicians a strong first-line, monotherapy in patients with depression and comorbid conditions.

In light of biochemical and pharmacologic data suggesting the utility of SSRIs in the treatment of multiple conditions, re-examination of traditional diagnostic categories and of ideas on the mode of action of antidepressants may be warranted.<sup>16</sup> In fact, some researchers<sup>3</sup> have predicted that drugs for mental disorders will cease to be categorized as antidepressants or anxiolytics, for example, and instead will be grouped according to their mode of activity (eg, SSRIs or MAO inhibitors).

#### Cost Effectiveness

Although the SSRIs may cost more than older antidepressants, their broad spectrum of activity makes them ideally suited for treating comorbid psychiatric disorders. Moreover, recent studies on depression indicate that, despite their higher prices, they are highly cost effective. For example, when overall consumption of healthcare resources, such as labor and follow-up physician visits for patient relapses, are considered, they may offer overall cost-effectiveness advantages over the older tricyclic antidepressants.<sup>18</sup> A study in the United Kingdom measured annual cost per successfully treated patient and found that paroxetine cost less than the tricyclic imipramine (£824 versus £1,024).<sup>19</sup> Another study<sup>20</sup> showed that the SSRIs may be more cost-effective than the tricyclic agents because their degree of patient acceptability is higher. That study reported higher side-effect drop-out rates in the tricyclic group, resulting in more frequent office visits and hospitalizations.

A second generation of serotonergic agents that are more selective to one of the seven known serotonin receptors in the brain is under development. (Other serotonin receptors are found throughout the body.) However, because of this increased specificity, the new psychotropic agents may be effective in the treatment of only one or two conditions.<sup>17</sup>

#### Conclusion

For clinicians, comorbidity complicates diagnosis and treatment of depressed patients who also suffer symptoms of anxiety, panic disorder, or obsessive-compulsive disorder. Clinical trials report efficacy against these comorbid conditions with drugs that are

serotonin specific, particularly the highly selective-serotonin reuptake inhibitors. The SSRIs allow physicians to use monotherapy when treating people with these comorbid conditions, with symptom improvement equal to that of older therapies, yet with fewer side effects and greater patient compliance.

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