Anxiety Disorders and Depression Comorbidity

Jonathan D. Huppert

Abstract

The chapter reviews cross-sectional and longitudinal epidemiological studies related to the co-occurrence of anxiety disorders and depression. Results suggest that anxiety disorders and depression tend to co-occur in 20% to 40% of patients. Explanations for increased co-occurrence considered include overlapping diagnostic criteria, genetics, neurophysiology, neurochemistry, negative affect/temperament, perceived control, interpersonal mechanisms, and biases in information processing. According to most levels of analysis, there is more overlap with GAD and depression while specific phobias have the least overlap. Finally, data on the impact of depression on pharmacological and psychological treatments for anxiety disorders are reviewed. More work is needed to clarify the multiple interactive processes likely at play in the co-occurrence of anxiety and mood disorders and their treatment.

Keywords: anxiety, comorbidity, depression, neurophysiology, phenomenology, psychopathology, treatment

[AuQ1]

Prevalence of Comorbidity

Individuals with anxiety disorders and comorbid depression have more chronic and severe anxiety symptoms, are more impaired, are at greater risk for suicide, and utilize more services than those without depression (de Graaf et al., 2004). Not only is the impact on the individual significant, but the prevalence of comorbid anxiety and mood disorders is very high. Given the impact on patients and the health care system, it is essential to understand the nature of this comorbidity. One of the core questions is whether anxiety and depression are separate entities or better subsumed under the rubric of negative affect or neuroticism (see Mineka, Watson, & Clark, 1998; Wittchen et al., 2000). Significant efforts have been made to understand the similarities and differences between anxiety and depression at the symptom and affect (Mineka et al., 1998),

cognitive (Mathews & MacLeod, 2005), behavioral genetic (Middeldorp et al., 2005), specific genetic (Leonardo & Hen, 2006), psychophysiological (McNaughton & Corr, 2004), and neurochemical levels (Heim & Nemeroff, 2001). This chapter reviews the research on comorbid anxiety disorders and depression, while raising some methodological and clinical issues relevant to future research.

Prior to examining various approaches to understand the comorbidity of anxiety and depression, it is useful to examine the actual rates of comorbidity among anxiety and depressive disorders in clinical and epidemiological studies (for an earlier review, see also Mineka et al., 1998). While the emphasis of this chapter is depression occurring in the context of primary anxiety disorders, it is also useful to consider the prevalence of anxiety disorders in the context of depression. Lifetime diagnoses fail to

distinguish co-occurring diagnoses from the history of a resolved diagnosis and the presence of an additional diagnosis later in life, leading to potentially inflated estimates (also see Kraemer, Wilson, & Hayward, 2006, regarding "pseudo-comorbidity" in lifetime diagnoses). Therefore, this chapter focuses on rates of concurrent comorbidity. The National Comorbidity Survey (NCS) (Kessler, 2006a; Kessler et al., 1994) and the National Cormorbidity Survey Replication (NCS-R) (Kessler et al., 2005) in the United States, as well as two large clinical studies (Brown et al., 2001; Rush et al., 2005) provide exemplary data on the prevalence of major depressive disorder (MDD) or dysthymia in anxiety disorders and the prevalence of anxiety disorders in MDD or dysthymia (see Table 1). Most data on the NCS and NCS-R were examined through analysis of the original datasets (Kessler, 2006a, 2006b) for the purposes of this chapter. Given NCS base rates of current MDD in the general population of 4.9%,

and of dysthymia of 1.5%, the risk for a depressive disorder in the context of an anxiety disorder ranges from 5 to 8 times greater than the general population (all $ps < .01$). In addition, the NCS (Kessler, 2006a) reported 1-month prevalence rates of anxiety disorders as follows: 5.5% for specific phobia (SP), 1.4% for panic disorder (PD), 4.5% for social anxiety disorder (SAD), 1.6% for generalized anxiety disorder (GAD), and 2.1% for posttraumatic stress disorder (PTSD). The NCS-R yielded similar results (Kessler, 2006b): The base rates of current major depressive episode in the general population were 3.1%, and dysthymia was 1.2%, and the 1-month prevalence rates of anxiety disorders as follows: 6.3% for SP, 1.0% for PD, 3.5% for SAD, 1.6% for GAD, and 1.7% for PTSD. Risk for depression in the context of anxiety disorders were similar to the NCS (all $ps < .01$). Including the 12-month prevalence of obsessive-compulsive disorder (OCD) from the NCS-R of 1.0% (Kessler et al., 2005) as a proxy for

Table 1. Prevalence of Co-occurring Anxiety Disorders and Depressive Disorders in Epidemiological and Clinical Samples

	Specific Phobia	Panic Disorder	Social Anxiety Disorder	Generalized Anxiety Disorder	OCD	PTSD
% MDD in Anxiety Disorders						
NCS	26%	40%	24%	39%	N/A	36%
NCS-R	14%	34%	20%	35%	N/A	27%
Brown et al.	21%	30%	32%	29%	35%	65%
% Anxiety Disorders in MDD						
NCS	29%	12%	22%	12%	N/A	15%
NCS-R	28%	11%	23%	17%	N/A	14%
Brown et al.	17%	46%	43%	57%	18%	10%
STAR*D	N/A	9%	29%	21%	13%	19%
% Dysthymia in Anxiety Disorders						
NCS	7%	12%	5%	22%	N/A	13%
NCS-R	8%	19%	11%	17%	N/A	16%
Brown et al.	12%	9%	17%	6%	11%	20%
% Anxiety Disorder in Dysthymia						
NCS	25%	12%	16%	24%	N/A	19%
NCS-R	39%	16%	31%	22%	N/A	22%
Brown et al.	23%	34%	56%	50%	14%	8%

Note. MDD = Major Depressive Disorder; OCD = Obsessive-Compulsive Disorder; PTSD = Posttraumatic Stress Disorder; NCS = National Comorbidity Study (Kessler, 2006a); NCS-R = National Comorbidity Study-Replication (Kessler, 2006b); STAR*D (Rush et al., 2005); Brown et al., 2001; N/A = not available. Hierarchical exclusion criteria for GAD and depression were not utilized to obtain these estimates.

HUPPERT 577

3070-100_044.indd 577 5/26/2008 5:14:57 PM

current OCD, there appears to be a 3 to 20 times increased risk of having an anxiety disorder if one has a mood disorder (all $ps < .01$).

Given the increased risk for comorbidity of mood and anxiety disorders, there are a number of explanations of why mood and anxiety disorders may co-occur (cf., Middeldorp et al., 2005). These include (1) overlapping diagnostic criteria, (2) one disorder being an epiphenomenon of the other, (3) the disorders are different phases of an underlying disorder, (4) one disorder is a risk factor for the other, (5) there are overlapping genetic and etiological processes, and (6) reciprocal causation. In the rest of the chapter, these possibilities are considered and the potential processes or causes for each possibility are discussed, followed by treatment implications.

Phenomenological/Descriptive Overlap and Distinguishing Features

One reason that depressive disorders may co-occur frequently with anxiety disorders is the overlap in symptoms as defined by the text revision of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM–IV–TR)* (American Psychiatric Association, 2000). There are symptom criteria for GAD, SAD, and PTSD that are also symptom criteria for MDD or dysthymia. There are fewer symptom criteria that overlap with PD, OCD, and SP. The common and distinct features are considered separately for each of the anxiety disorders.

GAD

Brown et al. (2001) reported that approximately 50% of patients with current dysthymia meet criteria for GAD if rule-out criteria are ignored. Symptom criteria that overlap between depressive disorders and GAD include fatigue, sleep disturbance, and poor concentration. These three symptoms are sufficient to meet physiological symptom criteria for the diagnosis of GAD. If an individual feels down and worries most of the time, and has these three other symptoms, he or she would potentially meet criteria for both GAD and dysthymia. In addition, uncontrollable worries may significantly overlap with depressive rumination, although one can distinguish between depressive rumination and anxious worry in that rumination is usually past-focused while worry is usually future-focused (Watkins et al., 2005). However, it may be the case that uncontrollable negative thoughts about past and future are driven by similar processes and are therefore highly likely to co-occur (Watkins et al.,

2005). The considerable overlap of the symptoms of these disorders is taken into account in *DSM–IV–TR* through the exclusion criteria for GAD, which exclude the diagnosis if it occurs exclusively during the course of an MDD.

Despite the significant symptom overlap between GAD and depressive disorders, there are features that distinguish the two. Patients with GAD are likely to experience muscle tension and are not required to exhibit depressive affect; in fact, these patients report lower levels of depression than individuals who meet criteria for MDD (Brown et al., 1997). Uncontrollable worry is also a cardinal feature of GAD, while it is not a criterion for depressive disorders. Furthermore, there are cognitive phenomena such as estimation of impending threats or "loomingness" (Riskind & Williams, 2005), attentional biases toward threat (Mathews & MacLeod, 2005), and intolerance of uncertainty (Dugas, Schwartz, & Francis, 2004) that apply primarily to GAD. Similarly, certain cognitive styles or attitudes are particular to depression such as a personal, permanent, pervasive attribution of negative events combined with a sense of hopelessness (e.g., Alloy et al., 2006), and negative thinking styles (Dugas et al., 2004).

PTSD

Like GAD, PTSD also has many overlapping symptoms with depressive disorders. Some researchers (e.g., McWilliams, Cox, & Asmundson, 2005) have reported data supporting four symptom classes for PTSD, one being dysphoria (reexperiencing, avoidance, and hyperarousal are the others). The symptoms of dysphoria that overlap with depression include loss of interest, foreshortened future, feeling distant from others, irritability, and decreased concentration. In fact, the overlapping symptoms of both GAD and PTSD with depression have led Watson et al. (2005) to recommend a recategorization of the mood disorders to include both PTSD and GAD under the rubric of distress disorders. The fact that PTSD may lead to depression is consistent with psychological models of MDD, including helplessness/hopelessness (Alloy et al., 2006) and interpersonal models (Joiner & Coyne, 1999).

As with GAD, there are features of PTSD that distinguish it from depressive disorders. While trauma is common in depression and may even lead to MDD more frequently than to PTSD (McQuaid et al., 2001), it is not a necessary feature of depression, as it is for PTSD. Additionally, the reexperiencing, hyperarousal, and avoidance criteria are distinct from MDD. Furthermore, individuals with

PTSD have different characteristics, including cognitive processes (Harvey et al., 2004), and cortisol responses to stress (Heim & Nemeroff, 2001).

SAD

With SAD and MDD there is less immediate apparent overlap in diagnostic criteria, but there is considerable overlap in the characteristics not depicted as part of the diagnostic criteria. Depression has a strong interpersonal component (Joiner & Coyne, 1999). In addition, social anxiety and depression both tend to have lower levels of positive affect (see Watson et al., 2005). Finally, interpersonal rejection sensitivity, a characteristic of atypical depression, is clearly also an important aspect of SAD (see Schneier et al., 2003). In fact, Parker et al. (2002) have argued that atypical depression is not a distinct phenomenon, but rather is comorbid MDD and SAD.

A number of factors help differentiate SAD and MDD. Phenomenologically, most SAD patients avoid social situations for fear of negative feedback from others, while depressed individuals are more concerned with negative self-evaluations. Furthermore, individuals with SAD become anxious when experiencing symptoms of arousal or blushing, while these are not major concerns with patients with MDD. Individuals with SAD can show interest in many topics and do not necessarily exhibit elevated levels of sadness or hopelessness. In addition, social anxiety is characterized by thoughts of negative evaluation, embarrassment, criticism, and rejection, while depression is characterized by thoughts of loss, deprivation, pessimism, guilt, worthlessness, and failure (e.g., Cho & Telch 2005). And SAD is uniquely characterized by overestimated probabilities and costs of negative social events, and underestimation of social competence (Harvey et al., 2004). Furthermore, there are multiple studies suggesting early biased attention to threat in social anxiety, but not in depression (Harvey et al., 2004). In fact, depression may even reduce the presence of earlier biases in patients with SAD (Harvey et al., 2004).

PD

Like SAD, PD does not have symptom criteria that explicitly overlap with depressive disorders. One factor that can complicate the differentiation of MDD and PD is that patients with MDD are at risk of having panic attacks during depressive episodes, without meeting criteria for PD. For example, among individuals in the NCS who did not have lifetime panic disorder, 6% of patients with a 1-year diagnosis of MDD reported having had panic attacks in the last 6 months, compared to only 1.3% of individuals without MDD. In addition, panic attacks have been shown to be a risk factor for the later development of MDD (e.g., Bittner et al., 2004). These issues notwithstanding, the distinction between PD and MDD is typically straightforward. In addition to symptom criteria, there are distinctions in PD compared with MDD in the types of thoughts and cognitive processes that occur (Woody et al., 1998), responses to panic challenges (e.g., Kent et al., 2001), and HPA axis responses (e.g., Kellner & Yehuda, 1999).

OCD

Obsessive-compulsive disorder, like panic disorder, is typically quite distinct from depressive disorders, even though there are high rates of comorbidity. There are neurobiological data suggesting that selective serotonin reuptake inhibitors (SSRIs) may act in different, specific areas of the brain in OCD compared with depression (Saxena et al., 2002). In addition, depression responds to non-SRI tricylic antidepressants whereas OCD does not (McNaughten & Coor, 2004). Two characteristics of MDD may be confused with OCD symptoms. First, depressive rumination may be confused with obsessions. This confusion is partially a semantic issue—colloquially, many individuals describe repeated thoughts as "obsessing," and therefore a depressed patient may describe being obsessed about the past. However, in order for guilt or past deeds to meet the criteria of obsessions, they should be consistent, repetitive thoughts, possibly followed by compulsions. In addition, OCD patients with thoughts of harming themselves or others may be considered depressed and suicidal. While many of these individuals are depressed about having these thoughts, there is no necessary relationship between self-harm obsessions and depressive thoughts.

SP

Typically thought to have the least overlap with depression, specific phobia is a fear disorder that does not usually include nonspecific levels of anxiety that are commonly related also to depression. Little research has been conducted examining the commonalities and distinctions in SP and MDD. However, cognitive processes in SP are similar to those in other anxiety disorders (Harvey et al., 2004), and some of these processes such as early attention to threat are not found in depressed individuals. In addition, SSRIs are not effective for SP

whereas benzodiazepines, which are sometimes used clinically for specific phobias, are not effective for MDD (McNaughten & Coor, 2004).

Overall, it seems that symptom overlap may account for part of the prevalence of comorbidity in GAD, PTSD, and SAD, but it is less likely to account for comorbidity in PD, OCD, and SP. Anxiety disorders are characterized by apprehension about and hypervigilance for physical or social threat, cognitive biases toward these threats, response to benzodiazepines, SSRIs, and medications that act on multiple neurotransmitter systems (e.g., norepinephrine, serotonin), some differential metabolic changes when administered SSRIs, and certain differences in HPA-Axis responses. Thus, most levels of analysis suggest that while anxiety disorders and depression co-occur, they are distinct disorders.

Time Course of Comorbid Anxiety Disorders and Depression

Many discussions of comorbidity of anxiety disorders and depression have examined the temporal relationship between the two and have concluded that anxiety disorders frequently precede depression (e.g., Andrade et al., 2003; Mineka et al., 1998). It is important to note that these data are necessary but not sufficient to suggest causality. It is likely that many factors play a role in the temporal relationship of the disorders, including the age of onset. For example, Brown and colleagues (2001) found that in 68% of SAD, 64% of SP, 62% of GAD, 36% of PTSD, 49% of OCD, and 31% of PD patients, the onset of MDD occurred after the onset of the anxiety disorder. However, the average age of onset of MDD was 26.4, and average age of onset for anxiety disorders ranged from 15.7 (SAD) to 26.0 (PD). The correlation between age of onset of the anxiety disorder and the percentage of comorbid individuals for whom anxiety preceded depression is $r = -.83$ ($p < .05$), suggesting that age of onset itself strongly influences temporal relationships. Of course, these data need to be taken in the context of the significantly increased risk of depression in anxiety, which increases the likelihood of a true association (though causality requires further evidence). An additional analysis to examine the directionality of the impact of depression and anxiety is to determine whether the onset of depression is earlier for individuals with lifetime histories of anxiety disorders, suggesting that anxiety disorders influence the course of depression. A reexamination of data from the NCS (Kessler, 2006a) for the purpose of this chapter found that age of onset for MDD was typically 1 to 2 years earlier in patients with comorbid MDD and anxiety disorders except for GAD, for which the age of onset for MDD was the same for patients with and without GAD (all other ps < .001). Average age of onset for MDD without an anxiety disorder was approximately 24 years old, but compared with MDD and a comorbid anxiety disorder was as follows: SP = 22.0 +/− 9.6, PD = 21.7 +/− 8.9, SAD = 21.9 +/− 9.8, PTSD = 21.0 +/− 9.8, GAD 23.2 +/− 8.9. On the other hand, lifetime MDD did not affect the age of onset for SAD or PTSD (ps > .05), though it did affect GAD ($p < .01$), SP ($p < .05$), and PD ($p < .05$), although the latter effect sizes were extremely small.

In addition to affecting age of onset, do anxiety disorders constitute an increased risk for onset of MDD longitudinally, and if so, what are the aspects of anxiety disorders that lead to the onset of depression? In a retrospective analysis, Zisook et al. (2004) found that individuals with an age of onset of MDD before 18 were more likely to have OCD or PTSD than those with MDD onset after age 18. Goodwin (2002) examined the risk of onset of MDD from the first to second waves of the Epidemiological Catchment Area (ECA) study. Each of the anxiety disorders examined (OCD, SP, agoraphobia, and panic attacks) all independently contributed to the onset of MDD in the second wave of the ECA, even when adjusting for other mental illness and demographic factors. Merikangas et al. (2003) found individuals with anxiety disorders were at increased risk of developing comorbid depressive disorders or depressive disorders alone. In addition, they found that individuals with comorbid anxiety and depressive disorders were very likely to be stable over time. Bittner et al. (2004) found that each of the anxiety disorders created increased risk for onset of a depressive disorder even when controlling for other disorders, except that SP alone did not confer an increased risk. Aspects of anxiety disorders that led to increased risk for development of depression included the number of anxiety disorders, severity of impairment, frequency of avoidance, and presence of panic attacks (Bittner et al., 2004; Wittchen et al., 2000). In contrast to these findings, Pine et al. (1998) found that SP and SAD did not confer elevated risk of onset of depression, but depression did confer an increased risk for later onset of GAD.

A few longitudinal, epidemiological studies have examined other characteristics that may lead to the development of comorbid anxiety and depression. Wittchen et al. (2000) found that additional risk

factors, including low school attainment, poor intimate relationships, overprotective family, early separation from a parent, chronic stress, temperament, and parental history of mental disorders, all contributed to the onset of comorbid anxiety and MDD. De Graaf et al. (2004) examined 3-year follow-up data from an epidemiological study and determined risk factors for development of comorbid mood and anxiety disorders beyond either a pure mood or pure anxiety disorder. Risk factors for the development of a mood disorder in the anxiety disorder group included childhood trauma, negative life events, and physical functioning.

Theories of Comorbidity

Given the evidence that individuals with anxiety disorders often have co-occurring depression, that this co-occurrence does not appear to be solely due to symptom overlap, and that the onset of anxiety disorders typically precedes the onset of depression, it is worth examining possible reasons for comorbidity. Approaches to understanding comorbidity have attempted to understand symptom and syndrome overlap on different explanatory levels, from biology to personality characteristics, cognitions, and behaviors. These approaches are not necessarily contradictory. Most of these explanations assume common underlying predispositions to both anxiety and depression.

Genetics

Twin and family studies that examine heritability of depression and anxiety have implicated specific genes in comorbidity. However, there is consensus that there is not a single gene that is involved in the development of comorbidity, but rather a series of polygene-environment interactions.

Family and twin studies have found different degrees of relationship between each of the anxiety disorders and major depression. The strongest evidence exists between GAD and MDD (see Middeldorp et al., 2005, for a review), though reasonable evidence exists for the genetic risk for comorbidity of anxiety disorders and depression overall. Some studies suggest that this underlying vulnerability may lie predominantly in personality traits such as neuroticism, while others suggest that anxiety disorders increase the risk for depression (and possibly that MDD increases the risk for GAD). After a thorough review of the literature on twin and family studies, Middeldorp et al. (2005) concluded that anxiety disorders and MDD are distinct entities, but that neuroticism appears to be a common

underlying vulnerability, and that it is possible that neural interconnections that are not involved in neuroticism may play a role in comorbidity.

One of the genes that has received particular emphasis is the serotonin-related gene (5-HT1A and 5-HTT; see Leonardo & Hen, 2006, for a review of these and others, including TPH; see also McNaughton & Corr, 2004). Polymorphisms in the 5-HT1A gene have been related to presence of anxiety and depression, and the 5-HTT gene is implicated in the mediating effects of SSRIs, which are generally effective for both mood and anxiety symptoms. In addition, a polymorphism in the 5-HTT gene (the double short version) has been related to the development of depression under stress (Caspi et al., 2003), and to a number of personality and psychological variables related to anxiety and depression such as anxiety sensitivity, harm avoidance, and neuroticism (see Leonardo & Hen, 2006, for a review). Finally, individuals with this gene also show greater amygdala activation under stress, and a disconnection between the amygdala and cingulate (Hariri et al., 2005), two areas implicated in anxiety and depression.
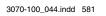
Neurophysiology

The prefrontal cortex, amygdala, and anterior cingulate have been implicated in both anxiety and depressive disorders (see Chapter 9; Liotti, & Mayberg, 2001). The amygdala is implicated as the emotional center of the brain and has been shown to play an important role in both anxiety and depression. Similarly, the prefrontal cortex appears to be generally underactive in anxiety and depression, though it may be overactive during rumination, obsessions, and worry (Chapter 9). There are also data showing decreased hippocampal volumes in individuals with PTSD and individuals with MDD (Heim, & Nemeroff, 2001).

Neurochemistry

In addition to a hypothesized overlap of serotonin deficiency in anxiety and mood disorders (McNaughton & Corr, 2004), there are other neurotransmitters and factors that are implicated in comorbidity. Similar to the work on genetics, the neurochemistry of mood and anxiety disorders is also increasingly based on interactions with the environment. For example, cholecystokinin (CCK) and endogenous opioids interact to relate to depression and anxiety (Hebb et al., 2005). In addition, significant emphasis has been placed on stress during early development and its relationship

to the dysregulation of the hypothalamic pituitary adrenocortical (HPA) axis (see Heim & Nemeroff, 2001). There have been certain aspects of the HPA axis that distinguish anxiety disorders (especially PTSD) from depression such as response to dexamethasone suppression tests, circadian plasma cortisol, overall cortisol levels, and glucocorticoid receptor binding (Kellner et al., 1999). However, increased release of corticotrophin releasing factor (CRF) and decreased adrenocorticotropic hormone (ACTH) responses to CRF are similar in anxiety and depression. The majority of studies have examined the HPA axis in relation to PTSD and major depression (for a review on the role of hormonal factors in anxiety disorders, see Chapter 10).

Neuroticism/Extraversion, Negative and Positive Affect, and Temperament

One of the most common explanations for the overlap of anxiety disorders and depression is the common underlying personality trait of neuroticism. Significant research has been conducted showing that individuals with elevated neuroticism are at greater risk for both anxiety and mood disorders (e.g., Weinstock & Whisman, 2006). Another common personality construct is that of introversion/extraversion, which has been related more to depression and social anxiety, but not to other anxiety disorders. Personality researchers have increasingly compared the traits of neuroticism and introversion/extroversion to the constructs of negative and positive affect (Watson et al., 2005). Multiple reports have suggested that negative affect is common to both anxiety disorders and depression while lack of positive affect is related more specifically to SAD and depression (Watson et al., 2005). Some epidemiological and genetic studies have begun to investigate whether the co-occurrence of anxiety disorders and depression is accounted for by neuroticism (e.g., Middeldorp, et al., 2005). These studies suggest that neuroticism clearly contributes to comorbidity, but that there continues to be increased risk for co-occurrence even after controlling for neuroticism. Overall, the data support the view that neuroticism or negative affect is an important component of the commonalities among the anxiety disorders and depression. More research is needed to determine the role of other factors such as anxiety sensitivity.

Within the sphere of developmental and personality theories, behavioral inhibition and behavioral activation have also been examined within the context of understanding comorbidity (Clark, 2005). Specifically, behavioral inhibition is suggested to be an early determinant of neuroticism and negative affect. Examinations of behaviorally inhibited children suggest they are at risk for later developing social anxiety (see Chapter 11. While some data do not support the notion of behavioral inhibition as a risk factor for depression, other research has suggested that a similar construct is related to anxiety and depression (Neal et al., 2002). It is likely that a global construct of behavioral inhibition is related to most anxiety disorders and to depression (Clark, 2005; McNaughton & Corr, 2004).

Perceived Control

Barlow and colleagues have noted that anxiety **[AuQ2]** disorders commonly precede depressive disorders, and that lack of perceived control over threat leads to a feeling of helplessness and hopelessness (see Chapter 13). Similarly, Alloy et al. (2006) have noted as part of the helplessness/hopelessness model of depression that anxiety often precedes depression. They propose that underlying comorbid anxiety and depression is a lack of certainty about negative outcomes (leading to anxiety) and a feeling of being unable to control the outcome (helplessness leading to depression).

Interpersonal Mechanisms

As noted earlier, childhood trauma and adversity are risk factors for the development of anxiety and depression. In fact, one study found that approximately 30% of the overlap of anxiety and depression could be accounted for by childhood adversity (Brown, Harris, & Eales, 1996). Research on the development of social anxiety has suggested that parental hostility may be related to both negative social interpretations in social anxiety, and is a risk factor for depression (Taylor & Alden, 2005). It is likely that similar aspects of family function or (perceived criticism, hostility, etc.) play a role in most anxiety disorders (e.g., Chambless et al., 2001). Similarly, interpersonal interactions have been implicated in the maintenance of depression (Joiner & Coyne, 1999), GAD (Borkovec et al., 2002), PD (Carter et al., 1994), SAD (Taylor & Alden, 2005), and PTSD (Riggs et al., 1998). Whether the disturbances in interpersonal functioning are a consequence of neuroticism/behavioral inhibition or interact with such traits requires further examination. Regardless of whether interpersonal factors are common underlying features related to mood and anxiety disorders, their roles in maintenance and treatment are extremely important.

Information Processing Models

Information processing models also suggest that there are commonalities between anxiety disorders and MDD (see Mathews & MacLeod, 2005, for a review). Individuals with anxiety disorders and MDD tend to be more self-focused (Harvey et al., 2004), have recurrent negative memories, intrusive thoughts, selective attention to emotionally congruent stimuli, biased interpretations of ambiguous scenarios, and negative expectancies (Mathews & MacLeod, 2005). Thus, it is likely that there are underlying cognitive processes that are related to the manifestation of depression and anxiety. More recently, studies have begun to show that these cognitive biases may be predictive of or even causal in terms of their relationship to anxiety and depression (see Mathews & MacLeod, 2005).

Treating Comorbid Anxiety Disorders and Depression
Depression as a Predictor of Treatment Response

In general, patients with comorbid anxiety and depression have more severe anxiety symptoms. Severity of symptoms is usually a predictor of treatment outcome, and data do not consistently support the notion that depression affects treatment outcome above and beyond the increased severity of anxiety symptoms. However, a naturalistic study examining the course of anxiety disorders (SAD, PD, and GAD) found that presence of comorbid depression was a factor in decreasing the likelihood of remission of each of the disorders (Bruce et al., 2005).

Treating Comorbid Anxiety Disorders and Depression

Studies have suggested that medications such as SSRIs (e.g., Sonawalla et al., 2002) and venlafaxine (De Nayer et al., 2002) are effective in the treatment of both anxiety and depression. Psychosocial treatments, especially cognitive behavioral therapies (CBT), have also shown promise. However, CBT is usually more symptom-focused than medications and may require focus on both anxious and depressive symptoms to have a full effect (see Joorman et al., 2005). The following sections summarize the treatment outcome literature for each of the individual anxiety disorders.

Panic Disorder. The literature on panic and depression is much more fully developed than that for the other anxiety disorders (see Mennin & Heimberg, 2000). Many recent studies have not found major negative effects of depression on outcome in panic disorder (e.g., Barlow et al., 2000), and Tsao et al. (2005) found that that depression decreases even when the focus of treatment is solely on panic.

Social Anxiety Disorder. The largest randomized controlled studies of treatments of SAD have excluded patients with comorbid depression (see Ledley et al., 2005). Given the high rates of co-occurrence, more information is needed on the treatment of individuals with comorbid SAD and MDD. Data from noncontrolled trials suggest that depression adversely impacts outcomes in that patients either have less symptom change (Chambless et al., 1997) or remain more symptomatic and impaired (Erwin et al., 2002), even if they do experience change at similar rates to nondepressed patients (i.e., they started worse, had similar amounts of change, and ended treatment worse off than nondepressed patients). In addition, depressive symptoms may impact outcome and attrition, even if the patient does not meet the threshold for MDD per se (Ledley et al., 2005). In one of the few studies examining medication treatment for comorbid SP and MDD, Schneier et al. (2003) found that citalopram was an effective treatment for both anxiety and depressive symptoms in this population. More research in this area is required to determine the best treatment strategies for patients with comorbid SAD and MDD.

OCD. The literature on treatment of OCD and comorbid depression also suggests that only severe depression may negatively impact the course of treatment and outcome of CBT (Abramowitz, 2004), and that depression does decrease with CBT. Similar results have been found with medication treatments. However, it may be that combined medication and CBT is the best option for comorbid OCD and MDD patients. More research is needed in this area.

GAD and PTSD. Given the diagnostic overlap of depression and GAD and depression and PTSD, relatively few studies have examined the impact of depression as a predictor of outcome on these disorders. In fact, a review of the literature found only case studies. However, depression has not been found to be a predictor of treatment outcome in either medication or psychosocial treatments, and many studies have found that depression is significantly reduced with treatment (e.g., Borkovec et al., 2002; Foa et al., 2005). There have been open label pharmacological studies of comorbid depression and GAD suggesting efficacy (Perugi et al., 2002), but there are no reports

on psychosocial treatments for comorbid MDD and GAD or PTSD. However, both medication and psychosocial treatments show that treatment reduces both anxiety and depressive symptoms in patients with GAD or PTSD. Research regarding optimal treatment strategies (combined treatments, monotherapy, sequential treatments) for comorbid anxiety disorders and depression is required.

Summary and Conclusions

Overall, both MDD and dysthymia commonly co-occur with the anxiety disorders, affecting 20% to 40% of anxious patients. The pattern of comorbidity is somewhat different across the spectrum of anxiety disorders, with a particularly strong and distinct relationship between GAD and depression from phenomenological, epidemiological, genetic, and cognitive perspectives. Most other anxiety disorders show similar patterns, with the possibility that SP is most unique from MDD. Data are generally consistent with Barlow's hierarchical model of the anxiety disorders (see Mineka et al., 1998; Chapter 13), in which each of the anxiety disorders and depression contain unique components, but also common underlying negative affect. An integrative biopsychosocial model suggests that there are genetic commonalities between anxiety disorders and depressive disorders, with support from genetic data (e.g., 5-HTT) and twin/family studies. Psychosocial stressors such as early trauma impact upon these predisposing factors, and may lead to disrupted neuroendocrine functioning and prefrontal-cingulate-amygdala circuitry. These processes are potentially reflected by affective, cognitive, and behavioral responses that include early behavioral inhibition, increased negative affect, tendencies to interpret ambiguous scenarios negatively, avoidance, and impairment in many areas of functioning. Much work needs to be done to clarify the interplay of these various processes. Finally, current treatments for comorbid anxiety and mood disorders include SSRIs or atypical antidepressants, CBT, or their combination. However, randomized controlled trials examining the optimal treatments for these comorbid disorders have not been conducted, nor is it known whether combined treatments are necessary, or how to most effectively combine treatments (e.g., simultaneous versus sequential treatments).

References

Abramowitz, J. S. (2004). Treatment of obsessive-compulsive disorder in patients who have comorbid major depression. *Journal of Clinical Psychology: 60,* 1133–1141.

Alloy, L. B., Abramson, L.Y., Whitehouse, W. G., Hogan, M. E., Panzarella, C., & Rose, D. T. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology: 115,* 145–156.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

Andrade, L. H., Caraveo-Aduaga, J. J., Berglund, P., Bijl, R. V., de Graaf, R., Vollebergh, W., et al. (2003). The epidemiology of major depressive episodes: Results from the ICPE surveys. *International Journal of Methods in Psychiatric Research, 12,* 3–21.

Barlow, D. H., Gorman, J. M., Shear, M. K., & Woods, S. W. (2000). Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. *Journal of the American Medical Association, 283,* 2529–2536.

Bittner, A., Goodwin, R. D., Wittchen, H., Beesdo, K., Höfler, M., & Lieb, R. (2004). What characteristics of primary anxiety disorders predict subsequent major depressive disorder? *Journal of Clinical Psychiatry: 65,* 618–626.

Borkovec, T. D., Newman, M. G., Pincus, A. L., & Lytle, R. (2002). A component analysis of cognitive-behavioral therapy for generalized anxiety disorder and the role of interpersonal problems. *Journal of Consulting and Clinical Psychology: 70,* 288–298.

Brown, G. W., Harris, T. O., & Eales, M. J. (1996). Social factors and comorbidity of depressive and anxiety disorders. *British Journal of Psychiatry: 168*(Suppl. 30), 50–57.

Brown, T. A., Campbell, L. A., Lehman, C. L., Grisham, J. R., & Mancill, R. B. (2001). Current and lifetime comorbidity of the *DSM–IV* anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology: 110,* 585–599.

Brown, T. A., Korotitsch, W., Chorpita, B. F. & Barlow, D. H. (1997). Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. *Behaviour Research and Therapy: 35,* 79–89.

Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M., et al. (2005). Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: A 12-year prospective study. *American Journal of Psychiatry: 162,* 1179–1187.

Carter, M. M., Turovsky, J., & Barlow, D. H. (1994). Interpersonal relationships in panic disorder with agoraphobia: A review of empirical evidence. *Clinical Psychology: Science and Practice, 1,* 25–34.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386–389.

Chambless, D. L., Tran, G. Q., & Glass, C. R. (1997). Predictors of response to cognitive-behavioral group therapy for social phobia. *Journal of Anxiety Disorders, 11,* 221–240.

Chambless, D. L., Bryan, A.D., Aiken, L. S., Steketee, G., & Hooley, J. M. (2001). Predicting expressed emotion: A study with families of obsessive-compulsive and agoraphobic outpatients. *Journal of Family Psychology: 15,* 225–240.

Cho, Y., & Telch, M. J. (2005). Testing the cognitive content-specificity hypothesis of social anxiety and depression: An application of structural equation modeling. *Cognitive Therapy and Research, 29,* 399–416.

Clark, L. A. (2005). Temperament as a unifying basis for personality and psychopathology. *Journal of Abnormal Psychology: 114,* 505–521.

De Graaf, R., Bijl, R. V., ten Have, M., Beekman, A.T.F., & Vollebergh, W.A.M. (2004). Pathways to comorbidity: The transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *Journal of Affective Disorders, 82,* 461–467.

De Nayer, A., Geerts, S., Ruelens, L., Schittecatte, M., De Bleeker, E., & Van Eeckhoutte, I., et al. (2002). Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. *International Journal of Neuropsychopharmacology: 5,* 115–120.

Dugas, M. J., Schwartz, A., & Francis, K. (2004). Intolerance of uncertainty, worry, and depression. *Cognitive Therapy and Research, 28,* 835–842.

Erwin, B. A., Heimberg, R. G., Juster, H., & Mindlin, M. (2002). Comorbid anxiety and mood disorders among persons with social anxiety disorder. *Behaviour Research and Therapy: 40,* 19–35.

Foa, E. B., Hembree, E. A., Cahill, S. P., Rauch, S.A.M., Riggs, D. S., Feeny, N. C., et al. (2005). Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: Outcome at academic and community clinics. *Journal of Consulting and Clinical Psychology: 73,* 953–964.

Goodwin, R. D. (2002). Anxiety disorders and the onset of depression among adults in the community. *Psychological Medicine, 32,* 1121–1124.

Hariri, A. R., Drabant, E. M., Munoz, K. E., Kolachana, B. S., Mattay, V. S., Egan, M. F., et al. (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry: 62,* 146–152.

Harvey, A., Watkins, E., Mansell, W., & Shafran, R. (2004). *Cognitive behavioural processes across psychological disorders.* New York: Oxford University Press.

Hebb, A.L.O., Poulin, J., Roach, S. P., Zacharko, R. M., & Drolet, G. (2005). Cholecystokinin and endogenous opioid peptides: Interactive influence on pain, cognition, and emotion. *Progress in Neuropsychopharmacology and Biological Psychiatry: 29,* 1225–1238.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry: 49,* 1023–1039.

Joiner, T., & Coyne, J. C. (Eds.). (1999). *The interactional nature of depression: Advances in interpersonal approaches.* Washington, DC: American Psychological Association.

Joormann, J., Kosfelder, J., & Schulte, D. (2005). The impact of comorbidity of depression on the course of anxiety treatments. *Cognitive Therapy and Research, 29,* 569–591.

Kellner, M., & Yehuda, R. (1999). Do panic disorder and posttraumatic stress disorder share a common psychoneuroendocrinology? *Psychoneuroendocrinology: 24,* 485–504.

Kent, J. M., Papp, L. A., Martinez, J. M., Browne, S. T., Coplan, J. D., Klein, D. F., et al. (2001). Specificity of panic response to CO_2 inhalation in panic disorder: A comparison with major depression and premenstrual dysphoric disorder. *American Journal of Psychiatry 158,* 58–67.

Kessler, R. C. (2006a). *National Comorbidity Survey: Baseline* [Computer file]. Conducted by University of Michigan, Survey Research Center. ICPSR06693-v4. Ann Arbor, MI: Inter-university Consortium for Political and Social Research.

Kessler, R. C. (2006b). *National Comorbidity Survey: Replication (NCS-R), 2001–2003* [Computer file]. Conducted by Harvard Medical School, Department of Health Care Policy/University of Michigan, Survey Research Center. ICPSR04438-v3. Ann Arbor, MI: Inter-university Consortium for Political and Social Research.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month *DSM–IV* disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry: 62,* 617–627.

Kessler, R. C., McGonagle, K. A., Zhao, S., & Nelson, C. B. (1994). Lifetime and 12-month prevalence of *DSM–III–R* psychiatric disorders in the United States: Results from the National Comorbidity Study. *Archives of General Psychiatry: 51,* 8–19.

Kraemer, H. C., Wilson, K. A., & Hayward, C. (2006). Lifetime prevalence and pseudocomorbidity in psychiatric research. *Archives of General Psychiatry: 63,* 604–608.

Ledley, D. R., Huppert, J. D., Foa, E. B., Davidson, J.R.T., Keefe, F. J., & Potts, N.L.S. (2005). Impact of depressive symptoms on the treatment of generalized social anxiety disorder. *Depression and Anxiety: 22,* 161–167.

Leonardo, E. D., & Hen, R. (2006). Genetics of affective and anxiety disorders. *Annual Review of Psychology: 57,* 117–137.

Liotti, M., & Mayberg, H. S. (2001). The role of functional neuroimaging in the neuropsychology of depression. *Journal of Clinical and Experimental Neuropsychology: 23,* 121–136.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology: 1,* 167–195.

McNaughton, N., & Corr, P. J. (2004). A two-dimensional neuropsychology of defense: Fear/anxiety and defensive distance. *Neuroscience and Biobehavioral Reviews, 28,* 285–305.

McQuaid, J. R., Pedrelli, P., McCahill, M. E., & Stein, M. B. (2001). Reported trauma, post-traumatic stress disorder and major depression among primary care patients. *Psychological Medicine, 31,* 1249–1257.

McWilliams, L. A., Cox, B. J., & Asmundson, G.J.G. (2005). Symptom structure of posttraumatic stress disorder in a nationally representative sample. *Journal of Anxiety Disorders, 19,* 626–641.

Mennin, D. S., & Heimberg, R. G. (2000). The impact of comorbid mood and personality disorders in the cognitive-behavioral treatment of panic disorder. *Clinical Psychology Review, 20,* 339–357.

Merikangas, K. R., Zhang, H., Avenevoli, S., Acharyya, S., Neuenschwander, M., & Angst, J. (2003). Longitudinal trajectories of depression and anxiety in a prospective community study. *Archives of General Psychiatry: 60,* 993–1000.

Middeldorp, C. M., Cath, D. C., Van Dyck, R., & Boomsma, D. I. (2005). The co-morbidity of anxiety and depression in the perspective of genetic epidemiology: A review of twin and family studies. *Psychological Medicine, 35,* 611–624.

Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology: 49,* 377–412.

Neal, J. A., Edelmann, R. J., & Glachan, M. (2002). Behavioural inhibition and symptoms of anxiety and depression: Is there a specific relationship with social phobia? *British Journal of Clinical Psychology: 41,* 361–374.

Parker, G., Roy, K., Mitchell, P., Wilhelm, K., Malhi, G., & Hadzi-Pavlovic, D. (2002). Atypical depression: A reappraisal. *American Journal of Psychiatry: 159,* 1480–1481.

Perugi, G., Frare, F., Toni, C., Ruffolo, G., & Torti, C. (2002). Open-label evaluation of venlafaxine sustained release in outpatients with generalized anxiety disorder with comorbid major depression or dysthymia: Effectiveness, tolerability and predictors of response. *Neuropsychobiology: 46,* 145–149.

Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry: 55,* 56–64.

Riggs, D. S., Byrne, C. A., Weathers, F. W., & Litz, B. T. (1998). The quality of the intimate relationships of male Vietnam veterans: Problems associated with posttraumatic stress disorder. *Journal of Traumatic Stress, 11,* 87–101.

Riskind, J. H., & Williams, N. L. (2005). The looming cognitive style and generalized anxiety disorder: Distinctive danger schemas and cognitive phenomenology. *Cognitive Therapy and Research, 29,* 7–27.

Rush, A. J., Zimmerman, M., Wisniewski, S. R., Fava, M., Hollon, S. D., Warden, D., et al. (2005). Comorbid psychiatric disorders in depressed outpatients: Demographic and clinical features. *Journal of Affective Disorders, 87,* 43–55.

Saxena, S., Brody, A. L., Ho, M. L., Alborzian, S., Maidment, K. M., Zohrabi, N., et al. (2002). Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs. major depression. *Archives of General Psychiatry: 59,* 250–261.

Schneier, F. R., Blanco, C., Campeas, R., Lewis-Fernandez, R., Lin, S., Marshall, R., et al. (2003). Citalopram treatment of social anxiety disorder with comorbid major depression. *Depression and Anxiety: 17,* 191–196.

Sonawalla, S. B., Farabaugh, A., Johnson, M. W., Morray, M., Delgado, M. L., Pingol, M. G., et al. (2002). Fluoxetine treatment of depressed patients with comorbid anxiety disorders. *Journal of Psychopharmacology: 16,* 215–219.

Taylor, C. T., & Alden, L. E. (2005). Social interpretation bias and generalized social phobia: The influence of developmental experiences. *Behaviour Research and Therapy: 43,* 759–777.

Tsao, J.C.I., Mystkowski, J. L., Zucker, B. G., & Craske, M. G. (2005). Impact of cognitive-behavioral therapy for panic disorder on comorbidity: A controlled investigation. *Behaviour Research and Therapy: 43,* 959–970.

Watkins, E., Moulds, M., & Mackintosh, B. (2005). Comparisons between rumination and worry in a non-clinical population. *Behaviour Research and Therapy: 43,* 1577–1585.

Watson, D., Gamez, W., & Simms, L. J. (2005). Basic dimensions of temperament and their relation to anxiety and depression: A symptom-based perspective. *Journal of Research in Personality: 39,* 46–66.

Weinstock, L. M., & Whisman, M. A. (2006). Neuroticism as a common feature of the depressive and anxiety disorders: A test of the revised integrative hierarchical model in a national sample. *Journal of Abnormal Psychology: 115,* 68–74.

Wittchen, H., Kessler, R. C., Pfister, H., & Lieb, M. (2000). Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatrica Scandinavica, 102,* 14–23.

Woody, S. R., Taylor, S., McLean, P. D., & Koch, W. J. (1998). Cognitive specificity in panic and depression: Implications for comorbidity. *Cognitive Therapy and Research, 22,* 427–443.

Zisook, S., Rush, A. J., Albala, A., Alpert, J., Balasubramani, G. K., Fava, M., et al. (2004). Factors that differentiate early vs. later onset of major depression disorder. *Psychiatry Research, 129,* 127–140.

[AuQ1]: psychopathology is not specifically mentioned in the text; is this okay?
[AuQ2]: Please provide a date for Barlow and colleagues and ensure that there is a corresponding reference entry.