Studies at the interface between anxiety and depression

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STUDIES AT THE INTERFACE
BETWEEN
ANXIETY AND DEPRESSION

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**STUDIES AT THE INTERFACE
BETWEEN
ANXIETY AND DEPRESSION**

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof mr GPMF Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 16 juni 2004 om 12.00 uur

door

Dina Theodora Overbeek

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Introductory Section

1. FOREWORD

The subject of this thesis is situated at the interface between anxiety and depression. The term ‘interface’ has multiple meanings in different domains. ‘Interface’ commonly refers to a boundary between two things, but can also refer to the overlap, and interaction between two theories or phenomena. Anxiety and depression can be viewed as separate entities, but also as overlapping or interacting concepts. An interface serves a dual purpose: it separates as well as it connects. This is the central theme of this thesis.

Fear and sadness can be considered *normal* counterparts of *pathological* anxiety and depression. They both describe normal human affects that can turn into pathology, or formal psychiatric disorders. Anxiety disorders and depressive disorders are the most prevalent psychiatric disorders, not only as discrete psychiatric disorders, but also in combined conditions, in which symptoms of both disorders coexist. These ‘comorbid’ conditions are usually characterized by higher severity, treatment resistance, and worse prognosis (Rapaport, 2001; Lecrubier, 2001). Because of their high prevalence, and impact on treatment and quality of life, these disorders are of major clinical importance. However, psychiatric comorbidity has received little attention in clinical practice or research.

The term to describe co-occurrence of psychiatric disorders in several forms is ‘comorbidity’. It is frequently used, but inconsistently defined. Comorbidity is a complex and heterogeneous construct, with several meanings. It is originally derived from general medicine and refers to the existence of two (or more) separate disorders with their own etiology and pathophysiology, in the same patient. In psychiatry, the use of this construct is cause of serious concern (Bogenschutz and Nurnberg, 2000, Vella et al., 2000), which is partially explained by the nature of the current nosology in psychiatry. Classification systems used in psychiatry are generally not based on etiopathogenesis, but on a-theoretical, historically developed consensus agreements, and have been argued to largely lack empirical foundation (van Praag, 2000). The prevailing diagnostic systems in modern western psychiatry, DSM-IV and ICD-10, provide operational criteria to make psychiatric diagnoses from a surface-descriptive point of view, thereby enabling the exchange of knowledge in corresponding terms. These systems, however, have clear shortcomings related to the nature of their design. Diagnoses are assigned when a certain number out of a discrete list of symptoms is present. The list is rather arbitrary, and

many combinations of various symptoms can lead to similar diagnoses¹. Sometimes core symptoms between two disorders overlap². Moreover, subsequent versions of DSM and ICD provide modified criteria and skip hierarchical rules from earlier versions, which has lead to large variations in prevalence rates of individual disorders and of comorbidity figures³. To complicate matters even further, comorbidity has been defined differently in several studies. For example, comorbidity sometimes refers to concurrent diagnoses (*cross-sectional*), or to lifetime diagnoses (*co-syndromal*), or to syndromal conditions in combination with symptoms of another disorder (*syndromal-subsyndromal*), and even to two subsyndromal states (*subsyndromal mixed anxiety-depression*). Therefore, it is not surprising that these issues have led to much confusion around the concept of comorbidity (Barbee, 1998). In every single study, albeit a clinical naturalistic study or a large scale population survey, a strict definition of the term comorbidity as is applied, is required for a proper understanding of the study findings.

However, no science can do without classification; psychiatry needs systems like DSM or ICD. It is clear that the current classifications also had a positive influence on psychiatry. The value lies in their use as a descriptive and classificatory tool, although their scientific basis should not be overrated.

The studies on which this thesis is based were performed at the Academic Anxiety Center in Maastricht, an outpatient clinic for diagnosis and treatment of anxiety disorders. The majority of the presented studies are clinical epidemiologic by nature, and describe prevalence data and naturalistic treatment effect for anxiety disorders.

The introductory chapter of this thesis provides a review of epidemiological studies on DSM-IV defined anxiety disorders. This chapter describes the background for the subsequent chapters, which are centered on the theme of comorbidity of anxiety and depression. The focus of the two chapters in Section I is the prevalence of comorbid depression in clinical samples of panic disorder patients, and patients suffering from obsessive compulsive disorder. These studies also empirically assess the implications of comorbid depression

¹ A diagnosis of Major Depression can be made by the presence of depressed mood, weight loss, agitation, feelings of guilt and difficulty concentrating, or by the presence of anhedonia, hypersomnia, weight gain, fatigue and suicidal ideation.

² Dysthymia and Generalized Anxiety Disorder both share symptoms of poor concentration, fatigue and sleep disturbance.

³ In DSM-III and earlier versions diagnoses of panic disorder (PD) and depression could not be assigned to the same patient, as depression was higher in hierarchy. Thus comorbidity of these two disorders did not 'exist' before DSM-III-R. From then on comorbidity of PD and depression has been reported in a large number of studies.

for treatment outcome. This section is followed by the presentation of three clinical studies concerning associated features in panic disorder patients. The subject of the first of these studies is the occurrence of suicidal ideation in panic disorder patients, as previous studies have reported an elevated suicide risk in panic disorder. The second study focuses on subjective sleep complaints in panic disorder patients. The hypothesis that nocturnal panic attacks and comorbid depression are responsible for sleep difficulties is tested. The third chapter of Section II is a replication study, testing the predictive value of a high score on blood-injury phobia (-avoidance) for treatment outcome of panic disorder. Section III is an excursion into the laboratory, to test in an experimental condition the observation that panic disorder patients often report aggressive symptoms and mood changes during panic attacks. The CO₂ challenge paradigm, which originally was developed in our own laboratory (Verburg et al., 2001), has been frequently used as an experimental model for panic disorder. This paradigm has been effective in selectively provoking symptoms of a panic attack in predisposed subjects. The study uses this provocation method to assess aggressive and depressive feelings in addition to anxiety. Section IV of this thesis goes beyond DSM terms and its disputed validity. This chapter offers a conceptual approach to fear and sadness and discusses the relationship between anxiety and depression with reference to the evolutionary theories in psychiatry and a philosophical reflection.

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2. EPIDEMIOLOGY OF ANXIETY DISORDERS

T. Overbeek, E. Vermetten and E. Griez

In: Griez EJL, Faravelli C, Nutt D and Zohar J (Eds). *Anxiety Disorders: An Introduction to Clinical Management and Research*. Wiley & Sons, Chichester, 2001 pp 3-23

INTRODUCTION

Anxiety disorders have a high impact on daily life (illness intrusiveness) and cause a great deal of suffering for the individual patient (Antony et al., 1998). They also have a substantial impact economically and incur a great deal of expenditure by society as a whole. Greenberg et al. (1999) report a total of \$42.3 billion per year as direct and indirect expenses in the USA and there are no obvious reasons to assume that the picture for European countries would be very different (Costa e Silva, 1998; Martin, 1998).

In the last decades some large epidemiological studies have provided much information about the occurrence of psychiatric disorders in general and anxiety disorders in particular. The Epidemiologic Catchment Area (ECA) study and the National Comorbidity Survey (NCS) in the USA (both coordinated by the National Institute of Mental Health NIMH) and the Munich Follow-up study in Europe are examples of landmark studies in this field (Regier et al., 1990b; Kessler et al., 1994; Wittchen et al., 1992). The World Health Organization (WHO) Study on Psychological Problems in General Health Care can be considered as an intermediate stage between epidemiological and clinical studies, and provides information on prevalence rates of mental disorders in primary care in 14 different countries world-wide (Sartorius et al., 1996). Many other clinical studies of specific target populations have yielded much information. Clinical studies often reveal different prevalence rates and comorbidity figures from population-based surveys and this is partly due to selection bias and severity of symptoms, and diagnostic criteria and instruments used. Therefore, Angst et al. (1997) advocate using subthreshold syndromes to enhance further the validity of diagnostic systems. They state that if subthreshold syndromes (especially concerning depression and anxiety) were included in diagnostic systems, the coverage of treated cases would be improved by nearly a third.

All excellent existing studies notwithstanding, there are still many reasons to be careful in making clear statements about the prevalence of mental disorders. We are facing different studies conducted in different countries in various settings: findings cannot be easily compared or generalized. Epidemiological studies have often used different diagnostic instruments, different sampling procedures, different case definitions, different time frames for the diagnoses (e.g. lifetime, six-month prevalence or current diagnoses) and different severity ratings for diagnostic decisions (Wittchen et al., 1992). The reservations above show the need for caution when interpreting the results.

Knowledge about prevalence rates of mental disorder does not automatically imply what needs to be done. There is a discrepancy between the real occurrence of disorders and the need for treatment, or the possibility of finding

the most adequate treatment for a diagnosed condition. Some filters can be taken into consideration. The first filter is recognition and correct diagnosis by the general practitioner. It is estimated that about 50% of cases do not pass this filter. The second filter is the most adequate treatment of the diagnosed disease. Again, only half of the patients pass. When these two filters are taken together, only roughly about 25% of disordered subjects finally receive adequate treatment. In addition, for some disorders patients do not really need treatment, e.g. most specific phobias can be adequately dealt with by means of avoidance. This means that although specific phobias are much more prevalent than, for example, obsessive-compulsive disorder (11% and 2-3% respectively), obsessive-compulsive disorder (OCD) should have preponderance.

Anxiety disorders are by far the most common psychiatric disorders (25%), followed by major depression (17%) (Kessler et al., 1994). Lifetime prevalence rates for all anxiety disorders lumped together as found in the NCS are 19.2% for men, 30.5% for women (Kessler et al., 1994). There is a strong correlation between socio-economic status and anxiety disorders. The one year prevalence as based on ECA data is 12.6% for all types of anxiety disorders, compared to 14.6% lifetime (Regier et al., 1998).

A final important introductory caveat is the issue of comorbidity. Comorbidity between disorders quite dramatically complicates the interpretation of many studies. Even apart from the considerable comorbidity figures between the anxiety disorders themselves, comorbidity rates between anxiety disorders and depressive disorders are very high (especially panic disorder with agoraphobia, social phobia and OCD), ranging from 30% for co-existing in time to 60% lifetime. Comorbidity rates between, for example, generalized anxiety disorder (GAD) or post-traumatic stress disorder (PTSD), and other psychiatric disorders are even higher, about 80% for GAD and 90% for PTSD lifetime figures.

The comorbidity of anxiety disorders and depressive disorders in general practice is common, with the happy consequence that the chance of recognition and the likelihood of receiving treatment are increased (Sartorius et al., 1996). However, for the epidemiologist this is complicated further because there is also a substantial comorbidity between several medical conditions (e.g. cardiac, pulmonary, cerebrovascular, gastrointestinal, diabetes and dermatologic diseases) and anxiety disorders (especially panic disorder, GAD and agoraphobia) (Stoudemire, 1996).

In this chapter the epidemiologic findings from some large population-based surveys and some smaller but relevant clinical studies will be reviewed. In doing so, DSM-IV anxiety disorders are arranged by diagnostic category (APA, 1994).

PANIC DISORDER AND AGORAPHOBIA

According to DSM-IV panic attacks are defined as sudden spells of unidentified feelings consisting of at least four out of 13 symptoms as palpitations, chest strains, sweating, shortness of breath, feelings of choking, trembling, nausea, dizziness, paresthesias, chills or hot flushes, depersonalization or derealization, fear of dying or losing control. Although having panic attacks does not imply that the diagnosis of panic disorder (PD) can be made and isolated panic attacks are not diagnosed as a disorder, they are often associated with substantial morbidity and do have some clinical significance (Klerman et al., 1991).

In order to make a diagnosis of PD, additional criteria are that these attacks at least once have been unexpected, followed by at least one month of fearful expectation or concern about the consequences of an attack. In the DSM-IV criteria as to the frequency of the attacks (in DSM-III-R, APA 1984, three attacks in a period of three weeks) are abandoned.

PD is frequently followed (or accompanied) by agoraphobia. Agoraphobia in DSM-IV is defined as (a) fear of being in places or situations from which escape might be difficult or help might not be available, (b) these situations are avoided or endured with marked distress or the patient needs a companion, and (c) the fear is not better explained by another mental disorder.

As such, isolated panic attacks (as defined above) are quite frequent, estimated at 7-9% for lifetime prevalence rates, although rather heterogeneous figures come from different countries (Pélissolo and Lépine, 1998). The ECA study on panic by Eaton reports 15% of all respondents have had a panic attack in lifetime, 3% in the past month, while 1% of the subjects meet criteria for PD in the past month (Eaton et al., 1994). In a survey among 1035 adolescents in Bremen, Germany, 18% of participants reported having had at least one panic attack (in a lifetime), with 0.5% of them meeting DSM-IV criteria for PD (Essau et al., 1999).

Prevalence

The prevalence of PD, assessed with diagnostic criteria and structured interviews, has been found in the majority of surveys to have lifetime rates between 1.5% and 2.5%. Twelve-month prevalence rates are generally about 1% (Pélissolo & Lépine, 1998).

Although PD can be diagnosed apart from agoraphobia, in clinical practice it is rare to find a patient suffering from PD who did not develop agoraphobia to a certain extent. This however is in contrast with the results from the NCS study, where it was found that 50% of PD patients report no agoraphobia (Eaton et al., 1994). Either way, it is infrequent to find an agoraphobic without a history of a panic attack. Horwath et al. (1993) have shown that epidemiologic studies that used the Diagnostic Interview Schedule and lay interviewers, such as the

ECA study, may have over-estimated the prevalence of agoraphobia without panic. The investigators took a sample of 22 ECA subjects diagnosed as having agoraphobia without panic attacks, and had them blindly reinterviewed. Reanalysis showed that only one of these subjects was left with the original diagnosis, one was assigned to having PD with agoraphobia, one had agoraphobia with limited symptom attacks, and the vast majority were reappraised as specific phobias (Horwath et al., 1993).

In addition, a recent study by Wittchen et al. (1998) in a community sample of 3021 young subjects (14 to 24 years) in Munich, Germany, addresses the relationship between PD and agoraphobia. They found that lifetime prevalence of PD with agoraphobia was as high as for PD without agoraphobia, both being 8%. Post hoc clinical review of the CIDI-positive agoraphobics revealed that many respondents did not have agoraphobia, but actually suffered from specific phobia, e.g. situational phobias. This resulted in a corrected agoraphobia prevalence of 3.5% instead of the original 8.5%. However, even after this correction, the majority of respondents with confirmed agoraphobia were found not to have a prior history of panic. However, in the NCS where agoraphobia was a separate diagnosis, it was found to have a lifetime prevalence rate of 6.7%, and a one-month prevalence of 2.3% (Magee et al., 1996).

Demographics and risk factors

Most studies reporting on PD or panic attacks consistently show higher rates for women than for men. Panic attacks are almost twice as common in women, whereas PD ranges from 1.5 to twice as much. The age at onset of PD in general lies in the mid-twenties, with hazard rates for women ranging from 25 to 35 years, for men between 30 and 45 years (Wittchen and Essau, 1993). Marital status is a significant risk factor for PD: the highest lifetime prevalence rates are found in widowed, separated or divorced subjects (Wittchen and Essau, 1993). On educational level and risk for developing PD there are no consistent findings, Eaton et al. (1994) report from the NCS data a tenfold higher risk for persons with less than twelve years of education. Several studies have suggested that life events such as early parental loss or childhood abuse may enhance the risk of PD, but there appears to be no specificity since this also applies to other psychiatric disorders as post-traumatic stress disorder and affective disorders.

Other supposed risk factors are smoking habits, although there is no consensus about causality or just correlation because all psychiatric patients smoke more than the general population. Breslau and Klein (1999) find evidence for smoking leading to PD. Others also indicate a role for smoking in developing PD (Pohl et al., 1992; Biber and Alkin, 1999; Amering et al., 1999). Another factor associated with PD is the existence of pulmonary disease. All conditions

that have symptoms of shortness of breath can lead to anxiety in general and PD in particular (Smoller et al., 1999). It is shown that respiratory disease in childhood (especially bronchitis and asthma) predisposes to PD in later life (Zandbergen et al., 1991; Verburg et al., 1995; Perna et al., 1997). Also, chronic obstructive pulmonary disorders can lead to PD in primarily lung patients (Wingate and Hansen-Flaschen, 1997), although the role of psychological factors, such as cognitive misinterpretation of bodily symptoms (e.g. shortness of breath) must be taken into account (Moore and Zebb, 1999).

Natural course

PD and agoraphobia seem to be a chronic condition, (Pollack and Smoller, 1995; Hirschfeld, 1996; Liebowitz, 1997) mostly with a fluctuating course with periods of waxing and waning (Liebowitz, 1997; Pollack and Otto, 1997). In some studies longitudinal aspects have been addressed, e.g. in a three-year follow-up only 10% were shown to be symptom free (Noyes et al., 1990). Faravelli et al. (1995) found that only 12% of PD patients after five years were in full remission. PD can be a very disabling disorder with high impact on daily life and social, personal and professional functioning and put a great burden on quality of life, (Candilis and Pollack, 1997; Candilis et al., 1999).

Comorbidity

Comorbidity of PD and agoraphobia is very common, as the panic attacks are often viewed as the precipitating cause for agoraphobia to develop (Klein and Klein, 1989). From this perspective, it is unnecessary to speak of true comorbidity, because the PD with agoraphobia can be considered one disease entity. The comorbidity of PD with agoraphobia is reported ranging from 29.5% to 58.2%. In the NCS (Eaton et al., 1994) 50% of the PD patients had comorbid agoraphobia. Also, findings from the study of Wittchen et al. (1998), cited above, indicate that half of patients with PD also developed agoraphobic avoidance. There is also a high degree of comorbidity with other anxiety disorders, such as social phobia (20-75%, see Pélioso and Lépine, 1998) and GAD (20%), 14% for obsessive-compulsive disorder and 6% for post-traumatic stress disorder (Goisman et al., 1994).

The Munich Follow-up Study (Wittchen and Essau, 1993) also stresses the risk for PD patients of developing comorbid other psychiatric disorders. In more than half of the cases some comorbid disorder will develop over time. Major depression (Merikangas et al. 1996) is the most frequent comorbid diagnosis, 30-60% of PD patients suffer from a depressive disorder (Weissman et al., 1997). Most studies report a concurrent prevalence rate of about 30%, with lifetime prevalence of depression occurring in about 60% (Wetzler and Sanderson, 1995). Also, the NCS data have shown a lifetime prevalence of depression in PD patients of 55.6% (Kessler et al., 1998a). There are divergent

views about the order of onset in comorbid PD and depression. In the ECA analysis it is shown that onset of panic is first in about 30% of cases, onset of depression precedes in another 30%, and simultaneous onset occurs in 40% (Regier et al., 1998). Also, some clinical studies have shown similar figures about the order of onset in comorbid PD and depression (Stein et al., 1990; Lydiard, 1991). Other clinical studies report that the onset of PD was first in about two-third of comorbid cases (Hunt and Andrews, 1995). The clinical significance of comorbidity lies in the severity of symptoms at the outset (Andrade et al., 1994).

Substance abuse (alcohol, drugs and medication) is also a common comorbid disorder, in 36% of cases, according to ECA data (Regier et al., 1990a). Most frequently, these abuse disorders are supposed to be secondary to the PD, and can be interpreted as self-medication (Marshall, 1997; Merikangas et al., 1998; Swendsen et al., 1998). Some authors, however, dispute this; Katerndahl and Realini (1999) for example found that the majority of drug and alcohol abusers report that the abuse started before the onset of the panic attacks.

The comorbidity of PD with other general medical conditions is described in a review by Zaubler and Katon (1998). It is shown that PD is common in cardiac, gastrointestinal, respiratory and neurological disorders.

SPECIFIC PHOBIAS

Specific phobias are the second most common anxiety disorder, after social phobia. They are, however, less impressive because they are mostly less incapacitating than other anxiety disorders. A specific phobia is defined as a circumscribed, persistent, and unreasonable fear of a particular object or situation. Exposure to this phobic stimulus is associated with an acute and severe anxiety reaction. Although individuals with specific phobias recognize their fear is unrealistic, most adjust their lifestyle so that they can completely avoid or at least minimize this contact (Fyer, 1998). Within the specific phobia category there is considerable heterogeneity. In the DSM-IV, four subtypes are defined: animal phobias, situational phobias, blood-injury phobia, and nature-environment phobia. The first three have been differentiated on the basis of a combination of factors including age at onset, symptom response, heritability and biological challenges (Fyer, 1998; Verburg et al., 1994). On the separate position of the nature-environment phobia there is less consensus (Fyer, 1998).

Prevalence

The NCS rates for one-month and lifetime specific phobia are 5.5% and 11.3% respectively (Magee et al., 1996). Among women, fear of animals is most frequent; fear of heights is most prevalent in men (Curtis et al., 1998). In a study addressing blood-injury phobia a lifetime prevalence of 3.5% was found, and a

mean age at onset of 5.5 years. Also noteworthy is that none of the subjects had ever sought professional treatment (Bienvenu and Eaton, 1998).

Demographics and risk factors

Female to male ratio for specific phobia is 2.3:1. In the NCS females had a lifetime prevalence of 15.7% and men 6.7% (Kessler et al., 1994).

Natural course

Simple phobia appeared in a study by Goisman et al. (1998) to be a chronic illness of moderate severity for which behavioral treatment methods of recognized efficacy were infrequently being used. The number of fears, independent of type, predicts impairment and professional help-seeking (Chapman et al., 1993; Curtis et al., 1998).

Comorbidity

Simple phobia is highly comorbid with other disorders; 83.4% of persons with simple phobia reported at least one lifetime comorbid disorder (Magee et al., 1996). The other anxiety disorders and major depression are most frequent. Also, specific phobia is frequently diagnosed as a comorbid disorder in other anxiety disorders (Goisman et al., 1998).

SOCIAL PHOBIAS

In recent years social phobia has gained more professional and public interest and increasingly is being recognized as a real anxiety disorder for which treatment can offer an improvement of the patients' quality of life (Kasper, 1998). Social phobia (social anxiety disorder) usually is rather disabling, characterized by marked fear of performance, excessive fear of scrutiny, and fear of acting in a way that may be embarrassing. Most patients are oversensitive to the assumed opinion of others and have a low self-esteem, although they feel their fears are exaggerated and out of proportion. Going through the feared situations, or even anticipating them, most people suffer from physical symptoms like sweating, trembling or blushing, and these symptoms can become a trigger on their own to worry about social consequences. This all can lead to avoidance of many social situations, or they endure these situations with extreme anxiety or distress (Liebowitz, 1999). As in all cases of phobias, the individual recognizes that his or her fears are unreasonable.

Social phobia can be divided in two subtypes. The first is generalized social phobia (or complex social phobia), patients being anxious in most situations, concerning performance and interactional situations. The patient with non-generalized social anxiety disorder being scared of only one or two (usual

performance-related) social situations, such as public speaking, or other public performance, such as writing or eating in front of others (Stein and Chavira, 1998; Moutier and Stein, 1999). Both types, however, tend to be underdiagnosed and undertreated (Stein and Chavira, 1998). There are some differences between the subgroups; the generalized type has even less chance of spontaneous recovery than the non-generalized. In the generalized subtype there is a stronger genetic factor (Kessler et al., 1998b). The generalized subtype is usually more invalidating and carries a higher risk of comorbidity. Age of onset does not differ between the subtypes.

Differential diagnoses for social anxiety disorder are: major depression with social withdrawal, PD with social avoidance, agoraphobia, GAD, OCD, and body dysmorphic disorder. Another important disorder to differentiate from social phobia is the DSM-IV axis II avoidant personality disorder. Although often seen as comorbid disorder, it is becoming increasingly clear that much avoidant personality disorder as defined by DSM-IV merely denotes a subgroup of patients with axis I generalized social phobia (Moutier and Stein, 1999).

Prevalence

Among the anxiety disorders social phobia nowadays is considered the third most common psychiatric disorder (13.3%), exceeded in lifetime prevalence only by major depression (17.1%) and alcohol dependence (14.1%) (Kessler et al., 1994), at least in the United States according to the NCS data. Prevalence rates for social phobia have increased in last decades. Earlier surveys, based on DIS and DSM-III criteria gave figures ranging from 2% to 4% (Pélissolo and Lépine, 1998). The ECA survey, for example, found one-month prevalence of 1.3%, a six-month prevalence of 1.5% and a lifetime prevalence of 2.8% (Schneier et al., 1992). Subsequent studies, based on DSM-III-R criteria and CIDI-interviews which explore more abundant and diversified social situations, reveal more elevated lifetime prevalences for social phobia, between 4.1% and 16%. The NCS study found a one-month prevalence of 4.5% and a lifetime prevalence of 13.3% (Magee et al., 1996).

A study by Weiller and others (1996) conducted in a general health care setting revealed a one-month prevalence of 4.9%, and a lifetime prevalence of 14.4%. They also stress that social phobia is underdiagnosed by general practitioners, in only 24.2% of the social phobics a diagnosis of anxiety disorder was made. When occurring with a comorbid depression even fewer patients were diagnosed as having a social phobia, although the presence of a comorbid depression increased the chance of diagnosing a psychological disorder.

Nevertheless, it should be noted that in some epidemiologic studies conducted in the Far East much lower lifetime prevalences are found, about 0.5% (Lépine and Lellouch, 1995). It is unclear whether this occurs on account of a cultural

bias of response or because of true psychopathological cross-cultural differences.

Demographics and risk factors

Most surveys mention a slight preponderance of women in social phobia (1.5 times as many as men). The NCS reports lifetime prevalence for women of 15.5% and for men 11.1% (Magee et al., 1996). In a study specifically addressing gender differences in social anxiety disorder (Weinstock, 1999) the authors state that although women are more likely to have social phobia, men are more likely to seek treatment, possibly explained by differences in gender roles and social expectations. There seems to be a difference in feared items between men and women: concerns about eating in restaurants and writing in public were more common in men, problems with using public restrooms and speaking in public were more common in women.

Social phobia is more frequently found at a younger age (18 to 29 years), among the less educated, the single, and the lower socio-economic class (Schneier et al., 1992). The Weiller et al. (1996) study showed an unemployment rate of 9.3%, compared with 1.3% for the control group. Employment status was also poor in the ECA study; social phobics changed their jobs more often and showed more absenteeism (Davidson et al., 1993).

Natural course

Typically social phobia has an onset in puberty and is often preceded by a general shyness in early youth (Liebowitz, 1999). The natural course tends to be chronic, unremitting and in course of time increasingly complicated by comorbid disorders. Because of the early age of onset, the disorder strongly influences further psychological development, formation of relationships, educational choices and career perspectives (Davidson et al., 1993).

Comorbidity

As it is the case for PD, in social phobia as well, the comorbidity rate is high. Around 80% of social phobia co-exists with other disorders (Lepine and Pelissolo, 1996; Montgomery, 1998). In particular, lifetime depression is high, about 70%, as well as other anxiety disorders. PD was diagnosed in 49%, GAD in 32% and OCD in 11% of social phobics (Van Ameringen et al., 1991). However, this study only comprised 57 subjects. Analysis of a part of ECA data with 123 social phobics revealed that 11.6% of them had lifetime PD, 45% had comorbid agoraphobia, 60.8% had specific phobia, and 26.9% had GAD (Davidson et al., 1993). The data from the NCS showed comorbidity with PD in 10.9% of cases, with agoraphobia in 23.3%, GAD in 13.3% and specific phobia in 37.6% (Magee et al., 1996).

Because of the early onset of social phobia, most often (in 70% of cases) the comorbid disorders appear secondary to the social phobia (Schneier et al., 1992).

The relationship between social phobia and alcoholism is a complex one. Reported prevalence rates vary widely, due to differing definitions, and methodological differences (Lepine and Pelissolo, 1998). Most studies on social phobia in patients with alcohol problems, abuse or dependence, report prevalences about 10 to 20%. Studies addressing social phobic patients report alcoholism in about 14 to 40% of cases. The social phobia most often predates the onset of alcohol problems. Although many social phobia sufferers use alcohol in an attempt to self-medicate their distressing anxiety symptoms, it appears that alcohol can actually increase anxiety, and a cycle may develop in which the sufferer drinks in order to relieve increasing levels of anxiety (Lepine and Pelissolo, 1998).

OBSESSIVE COMPULSIVE DISORDER

Obsessive Compulsive Disorder (OCD) is defined as the presence of recurrent obsessions (persistent thoughts, impulses, or images) or compulsions (repetitive behavior or thought patterns induced in an attempt to prevent anxiety) that are excessively time-consuming (taking more than an hour a day) or cause marked distress or significant impairment. The subject recognizes that these patterns are excessive.

Differential diagnosis of OCD includes GAD, PD, phobias, compulsive personality disorder, and hypochondriasis. While many of these syndromes are characterized by intrusive thoughts, few have associated rituals. The complex tics seen in some patients with Tourette's syndrome may be difficult to distinguish from the compulsions seen in OCD, and, in fact, there is significant overlap in symptoms between the two disorders (Rasmussen and Eisen, 1992). Although the phenomenology of OCD appears to be quite diverse, with many distinct kinds of obsessions and compulsions, there are three important core features: abnormal risk assessment, pathologic doubt, and incompleteness. These features cut across phenomenological subtypes and may be useful in defining homogeneous subgroups with distinct treatment outcomes (Rasmussen and Eisen, 1992). Pigott (1998) also describes core features of OCD and subdivides them in two categories: altered risk appraisal versus need for complete-ness/symmetry.

Prevalence

For OCD prevalence figures have been gradually growing over the years, as is the case for social phobia. Formerly OCD was thought to be quite rare, as people did not easily request treatment due to fear or shame (Rasmussen and

Eisen, 1992). Recent epidemiological studies have shown a six-month prevalence rate of OCD of approximately 1% (Bebbington, 1998), to a lifetime prevalence rate of 2-3% (Hollander, 1997; Sasson et al. 1997), which means that OCD is much more common than previously suggested. Hollander (1997) calls OCD 'the hidden epidemic', where social phobia has been called 'the neglected anxiety disorder' (Liebowitz, 1999). An earlier cross-national study by Weissman et al. (1997), using DSM-III criteria, reports annual prevalence rates ranging from 1.1% in Korea and New Zealand to 1.8% in Puerto Rico. The only exception was Taiwan (0.4%), which has the lowest prevalence rates for all psychiatric disorders (Weissman et al., 1994).

Unfortunately one of the best epidemiological studies in the U.S.A. the NCS did not address OCD because the diagnostic instrument used (the CIDI) excluded these cases (Bebbington, 1998).

Demographics and risk factors

The cross-national collaborative study examined OCD in seven different countries and found rather consistent figures. Age of onset was mid-to-late twenties. Female to male ratio ranged from 1.2 to 3.8 (Weissman et al., 1994), but earlier studies (among which was the ECA) reported an equal sex-distribution.

In a study that specifically addressed gender differences in a clinical sample of OCD patients Castle et al. (1995) found a male to female ratio of 1:1.35. Mean age of onset for men was 22 years, for women 26 years. Mean age at assessment did not differ significantly, 32.8 years for men and 34.6 years for women.

Natural course

OCD has a chronic course, and few patients achieve true remission. Although symptoms may fluctuate over time, the disorder rarely is resolved spontaneously without appropriate treatment (Goodman, 1999). Full remission of OCD symptoms is rare, but episodic improvement in OCD symptoms is not uncommon (Pigott, 1998). In a 40-year follow-up of 122 OCD patients, Skoog and Skoog (1999) substantiated these generalities: 20% achieved complete recovery, 28% recovery with subclinical symptoms, another 35% still had clinical symptoms but did improve. Some 48% had OCD for more than thirty years.

Comorbidity

Depression is the most frequent complication of OCD, as reported in several studies (Black and Noyes, 1990). Comorbidity rates in reported studies vary widely, from 19% to 90% (Milanfranchi et al., 1995). Within this wide range, however, most epidemiological studies show that about one third of OCD

patients suffer from a lifetime depressive episode. In clinical populations, comorbidity rates are increasing to about two-thirds (Crino and Andrews, 1996). Rasmussen found that one third of OCD patients suffer from concurrent depression at referral, and two-thirds suffer from lifetime depression (Rasmussen and Eisen, 1994), a similar finding as in PD. One explanation of the discrepancy between clinical and nonclinical studies could be that many OCD patients only seek help when depressed, as suggested by Black and Noyes (1990). As to chronology, it is found that most often the onset of OCD is before the depression (38%), transition from depression to OCD occurs in only 11% of cases (Black and Noyes, 1990).

Personality disorders are frequently diagnosed in OCD, but may remit with effective antiobsessional treatment (Pigott, 1998). This questions the validity of the axis II diagnosis at the outset. Also, a study by Ricciardi et al. (1992) showed that among 17 patients with OCD and concomitant personality disorder, after treatment nine out of ten responders no longer met the personality disorder-criteria (Ricciardi et al., 1992).

OCD also co-exists with a number of other Axis I disorders including PD (54%, Crino and Andrews, 1996), social phobia (42%, Crino and Andrews, 1996), eating disorders (17%, Rasmussen and Eisen, 1994), and Tourette's disorder (5%, Black and Noyes, 1990). Crino and Andrews (1996) remark that the high comorbidity of PD and social phobia in OCD is in contrast to the low comorbidity of OCD in primary PD or social phobic patients. However, they did not find any different rate of comorbid depression among the anxiety disorders.

GENERALIZED ANXIETY DISORDER

The concept of generalized anxiety disorder (GAD) is subject to discussion. Although the disorder is regarded as prevalent in primary care as well as in specialized settings, because of the high comorbidity rates associated with GAD the controversy is about whether to consider GAD as a independent disorder or as a residual or prodrome of other disorders (Wittchen et al., 1994). The diagnostic category of GAD has changed a lot in the past two decades (Brawman-Mintzer and Lydiard, 1996). The shifting diagnostic criteria, the relative low diagnostic reliability, and questions regarding the diagnostic validity probably contributed to the relative little attention that has been paid to the investigation of GAD compared with most other anxiety disorders (Brawman-Mintzer and Lydiard, 1996).

Prevalence

The most recent epidemiologic study using DSM-III-R criteria is the NCS in the United States. The prevalence rate for current GAD was 1.6%, 12-month

prevalence was 3.1% and lifetime prevalence for GAD was 5.1% (Wittchen et al., 1994). These figures make GAD more common than PD in the NCS. It is shown that GAD is more common in primary care, and one of the least common anxiety disorders in mental health centers (Brawman-Mintzer and Lydiard, 1996).

Demographics and risk factors

GAD is twice as common among women as among men. In the age group between 25-35 years the prevalence is highest (Wittchen et al., 1994). Risk factors for GAD are being separated, widowed or divorced (the same risk factors as for PD), and also unemployment or being a homemaker is a significant correlate of GAD. However, another recent study (Bienvenu et al., 1998) suggests that being widowed is not a risk factor.

Natural course

GAD appears to have a chronic course. Woodman et al. (1999) conducted a five-year follow-up study comparing primary GAD patients to PD patients. At baseline the GAD subjects were significantly older, had a higher level of education and occupational class, earlier age of onset and longer illness duration. At follow-up, significantly more GAD patients continued to meet full criteria for the baseline disorder, and fewer were in partial or complete remission or had fluctuations. Although global severity, measured by clinical global impression (CGI), was less at baseline, at follow-up the improvement on the CGI was significantly less for the GAD patients compared with the PD patients. Findings from this study support the validity of the GAD concept, in view of the diagnostic stability and different natural course (Woodman et al., 1999).

Comorbidity

Lifetime comorbidity for GAD is very high, 90.4% of cases (Wittchen et al., 1994). The strongest comorbidities are with affective disorders (mania 10.5%, major depression 62.4%, dysthymia 39.5%). Comorbidity figures with other anxiety disorders are 23.5% for PD, 25.7% for agoraphobia, 35.1% for simple phobia and 34.4% for social phobia. Alcohol abuse and dependence was seen in 37.6% of cases and drugs in 27.6%. Another study by Brawman-Mintzer et al. (1993) reports comorbid social phobia in 23% and simple phobia in 21% of cases as the most frequent, after excluding lifetime depression. The high comorbidity figures have led to disagreement concerning the existence of GAD as an independent diagnostic entity, and to assumptions that GAD is a prodrome or residual of other disorders (Brawman-Mintzer and Lydiard, 1996). Also, at least partly the same genetic factors contribute to major depression and GAD, as shown by Kendler (1996). However, in the NCS it is shown that at

least 30% of current GAD patients had neither current nor recent (but only lifetime) comorbid disorders. This is put forward by the authors as supporting the validity of GAD as an independent diagnosis (Wittchen et al., 1994), although this does not preclude GAD from being a prodrome of any other disorder.

GAD is frequently seen in primary health care, and especially in patients with medically unexplained somatic complaints such as chest pain and irritable bowel symptoms (Roy-Byrne, 1996). As such, it is also associated with somatization disorder and chronic fatigue syndrome (Fischler et al., 1997). Comorbidity with axis-II disorders is also high, reported up to 49% (Sanderson et al., 1994).

POSTTRAUMATIC STRESS DISORDER

The DSM-IV definition for post-traumatic stress disorder (PTSD) contains criteria for (a) the traumatic experience; (b) re-experiencing; (c) avoidance of associated stimuli and numbing; (d) increased arousal. Duration of symptoms should be at least one month (e), and (f) distress or impairment in functioning is required (APA, 1994). When PTSD was first defined in DSM-III (APA, 1980) the original stressor criterion characterized traumatic experiences as being outside the range of human experience. However, when the prevalence of such events was systematically examined it became apparent that trauma is surprisingly commonplace. Several studies have investigated the overall prevalence of traumatic events in the general population looking both at community-based populations and populations of individuals at high risk for trauma or exposed to events such as natural disasters (Acierino et al., 1999). The nature of the trauma can be very diverse, such as childhood abuse, traffic accidents, fires, violent assault, robberies and floods or earthquakes.

Prevalence

Prevalence rates have increased from DSM-III to DSM-III-R and DSM-IV. Also, in some telephone interview surveys prevalence is much higher, and in studies among young persons where recall-bias may be minimal. Kessler et al. (1995) reported about the National Comorbidity Survey of 5877 persons, aged 15 to 54 years. The estimated lifetime prevalence of PTSD was found to be 7.8% (Kessler et al., 1995).

In routine clinical practice, PTSD is often underdiagnosed if the PTSD is not the presenting complaint, but an additional diagnosis (Zimmerman and Mattia, 1999). The same comment, however, can be made for other anxiety disorders, as social phobia (Kessler et al., 1999). Reasons for misdiagnosis of PTSD include a high rate of comorbidity, patient denial or minimization, overly high diagnostic thresholds set by clinicians, or failure to take a trauma history

(Davidson and Connor, 1999). In a cohort study of 185 persons involved in a traffic accident and a hotel-fire Maes et al. (1998) found after seven to nine months a prevalence of DSM-III-R PTSD of 23%. Almost 50% of them had symptoms the first day, about 70% developed PTSD symptoms during the first week after the event.

In one study, victims of substantiated child abuse and neglect were assessed and compared with a group of matched non-abused and non-neglected children and followed into adulthood. Victims of child abuse (sexual and physical) and neglect were found to be at increased risk of developing PTSD. More than a third of the childhood victims of sexual abuse (37.5%), 32.7% of those physically abused, and 30.6% of victims of childhood neglect, met DSM-III-R criteria for lifetime PTSD. Childhood victimization, however, is not a sufficient condition for developing PTSD, also family, individual, and lifestyle variables place individuals at risk and contributed to the symptoms of PTSD (Widom, 1999).

North et al. (1999) report on a follow-up on the terrorist Oklahoma City bombing in 1995 where a bomb blast killed 168 people. In their sample of 182 participating adults, 45% had a post-disaster psychiatric disorder and 34.3% had PTSD. The onset of PTSD was swift, with 76% reporting same-day onset. The relatively uncommon avoidance and numbing symptoms virtually dictated the diagnosis of PTSD (94% meeting avoidance and numbing criteria had full PTSD diagnosis) and were further associated with psychiatric comorbidity, functional impairment, and treatment received. Intrusive re-experiencing and hyperarousal symptoms were nearly universal, but by themselves were generally unassociated with other psychopathology or impairment in functioning (North et al., 1999).

Demographics and risk factors

NCS data showed that prevalence was elevated among women and the widowed, separated or divorced. The traumas most commonly associated with PTSD were combat exposure and witnessing of violence among men, and rape and sexual molestation among women.

A variety of factors influence response to trauma and development of PTSD. They include characteristics of the stressor and exposure to it (e.g. repeated trauma increases the risk); individual factors such as gender (females are at higher risk), age and developmental level (the younger are at higher risk), and psychiatric history, family characteristics, and cultural factors (Pfefferbaum, 1997).

Natural course

In the NCS survival analysis showed that more than one-third of people with an index episode of PTSD failed to recover even after many years (Kessler et

al., 1995). Among the subjects who had ever sought professional help (58% of affected respondents) the median time to remission was 36 months, among those who did not seek help the median time to remission was 64 months. A study of 61 Vietnam combat veterans with PTSD showed that onset of symptoms typically occurred at the time of exposure to combat trauma in Vietnam and increased rapidly during the first few years after the war. Symptoms plateaued within a few years after the war, following which the disorder became chronic and unremitting. Hyperarousal symptoms developed first, followed by avoidant symptoms, and finally by symptoms from the intrusive cluster. The onset of alcohol and substance abuse was associated with the onset of PTSD symptoms, and the increase in use paralleled the increase of symptoms (Bremner et al., 1996). Another recent study of Gulf War veterans showed that PTSD increases over time, two years after the war 8% of 2949 veterans developed a PTSD, compared with 3% immediately following the war (Wolfe et al., 1999).

Comorbidity

Post-traumatic stress disorder in the NCS findings was strongly comorbid with other lifetime DSM-III-R disorders. A lifetime history of at least one disorder was present in 88.3% of men, and 79% of women with lifetime PTSD (Kessler et al., 1995). Frequent comorbid diagnoses are: affective disorders (almost 50% of cases for major depression, 20% for dysthymia), other anxiety disorders (16% GAD, 9% PD, 30% specific phobia, 28% social phobia, 19% agoraphobia), substance use disorders (52% alcohol and 34% drugs in men, 28% alcohol and 27% drugs in women) and conduct disorder (43% in men and 15% in women) (Kessler et al., 1995), and somatization (McCauley et al., 1997).

CONCLUSION

The authors would like to end by the beginning, referring to the caveats mentioned in the introduction of the present chapter. There are still other matters of concern: the frequent use of lay interviewers in major surveys, recall bias in interviews over lifetime span, the key issue of defining a threshold for clinical significance, just to name a few. It follows that in spite of the apparent evidence, extreme caution should be exercised when interpreting the epidemiology of anxiety.

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*Section I. Prevalence of depression
in panic disorder and
obsessive-compulsive disorder*

3. COMORBIDITY OF DEPRESSION AND PANIC DISORDER

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INTRODUCTION

In 1984, one of the pioneering studies in the field of comorbidity between depression and panic ended with the following statements: ‘(1) major depression occurs in two thirds of patients who come to an anxiety disorders clinic with agoraphobia-panic disorder; (2) one half of these patients who have a history of major depression have at least one major depressive episode prior to and, in most cases, temporally separate from the onset of panic attacks; and (3) patients with agoraphobia-panic disorder with a history of major depression have a more severe anxiety disorder at the time of admission, greater levels of past impairment, and a longer duration of panic disorder as compared with patients with agoraphobia-panic disorder with no history of depression’ (Breier et al., 1984).

Since the publication of Breier et al. study, interest in the relationship between mood and anxiety disorders has continued to grow rapidly. Comorbidity, and particularly comorbidity between anxiety and depression, has become a favorite concept in the psychiatric literature. Accumulating evidence supports the view that there is a close link between major anxiety disorders and depression. Overall, studies show that, more than a decade later, the headlines of the Breier et al. (1984) findings still hold true.

However, the interpretation of this so-called comorbidity has become a matter of debate. Are we facing a phenomenon of true comorbidity, or is this new ‘evidence’ an artefact produced by present days diagnostic systems?

Basically, comorbidity refers to the presence of more than one disorder in one subject. Comorbidity has been defined as “any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study” (Feinstein, 1970). Ideally, each ‘clinical entity’ under consideration should be a true disease, which signs and symptoms are codified, and whose underlying mechanisms are well understood. In that case, the assessment of comorbid conditions is quite an easy task and there will be little room left for discussion whether, in a particular case, one should distinguish one or more diseases. However, pathogenic mechanisms of psychiatric conditions remain largely unknown. The codification of signs, symptoms and diagnostic criteria is largely a matter of consensus on basis of fragmentary knowledge (American Psychiatric Association, 1980, 1987, 1994). As long as this situation persists, the delineation of valid ‘clinical entities’ will be, at best, a series of good approximations. This is to say that the study of psychiatric comorbidity at present relies heavily on the acceptance of current diagnostic and classification systems.

Current diagnostic systems share a number of features. These features do condition comorbidity research. They may explain why comorbidity is better

recognized since these diagnostic systems came into force. On the other hand, they point to some important limitations with regard to the approach to comorbidity. A number of these features are of particular importance to the field of affective disorders.

Current diagnostic systems, such as DSM-III and its subsequent editions: (1) use a categorical approach based on operational criteria; (2) tend, in case of doubt, to split rather than to lump syndromes and refuse to establish hierarchies amongst them; (3) group anxiety disorders as a separate category with several subcategories.

Present-day psychiatric diagnosis is based on a categorical approach, following the medical tradition: one has or one has not a particular disorder. For each disorder, a number of operational criteria have been clearly defined. Moreover, structured interviews have become available. The emergence of well-defined diagnostic guidelines and the use of standardized interviews have facilitated the recognition of existing comorbid pathology previously neglected in presence of a more pervasive disorder and have favored a more complete screening of the patient's condition.

However, the multiplication of standardized screening instruments may engender an attitude of 'fishing for symptoms' with little consideration for clinical significance. There are no objective cut-off points for clinical anxiety and depression. In particular, insufficiently trained investigators may use very low threshold, and create an artificial high rate of comorbidity. Another problem when using standardized instruments is the halo effect: results in one section may be influenced by answers in the preceding section. For instance, positive findings in the anxiety section may influence the result in the mood section, and vice versa (Frances et al., 1992). The systematic use of structured interviews may give rise to very high rates of 'clinical' diagnoses, twice to three times as many as in routine assessment (Wittchen, 1996). It is possible that such incredibly high rates are vitiated by serious artefacts.

DSM-III, and still more DSM-III-R and DSM-IV, are splitters. The empirical and descriptive approach which underlies the system results in a multiplicity of diagnostic categories. In addition, there is lack of organizing principles, as a consequence of the scarce knowledge in the pathogenic mechanisms of most disorders. Thus numerous disorders may be diagnosed and, predictably, the more diagnoses, the higher the chance of comorbidity. The advantage of having a large number of clinical pictures potentially diagnosed is that they are recognized and may be put under the scrutiny of scientific investigation. In this sense, a lot of current DSM categories should be considered as working hypotheses. Regrettably, there is a danger of reification of current diagnostic categories without sufficient scientific validation. We may witness the proliferation of little-credible disorders. An additional limitation due to absence of hierarchical organization is that researchers are faced with an atomization of

clinical conditions, while differences in underlying mechanisms may not exist. In this case the concept of 'spectrum diseases' may be a good remedy. Since the publication of DSM-III, anxiety disorders have been grouped as a separate category, and split into several distinct disorders. While anxiety disorders previously tended to form an amalgam with the 'neuroses', they have now been recognized on their own, with clear-cut differentiations between panic disorder (PD), agoraphobia with panic, phobias, obsessive-compulsive disorder and post-traumatic disorder. What happened to the anxiety disorders is a beautiful example of an empirical process at work in the DSM approach. The decision to split anxiety neurosis and to delineate PD was largely inspired by the early clinical and experimental findings of D. Klein and his coworkers (1964). In turn, the definition of PD fostered its recognition. An impetus of research into this new entity followed, soon resulting in an impressive piece of scientific evidence in support of its validity. However, the present classification of anxiety disorders shows its limits as well. There has been a continuing debate about the relationship between panic and agoraphobia, and in particular, whether agoraphobia exists without panic attacks. Also, while PD has gained strong validity, the division of anxiety neurosis has left an ill-defined category under the name of generalized anxiety disorder (GAD). Most studies show comorbidity rates of 70-80% for GAD, strongly suggesting lack of validity. In sum, is psychiatric comorbidity 'fact or artefact' (Wittchen, 1996)? Undoubtedly, it is not merely a methodological artefact, as witnessed by the core of data in the following sections of this chapter. However, when accounting for the high rates of comorbidity which are found in recent studies, it should be borne in mind that the study of comorbidity relies on the way disorders are defined, and that current diagnostic systems are largely working hypotheses in need of validation. To this extent, the investigation of comorbidity in psychiatry will still be for years a difficult exercise.

PANIC AND DEPRESSION: AN OVERVIEW OF RECENT DATA

In clinical practice depression and anxiety often coexist. A considerable number of patients presenting with anxiety disorders have a comorbid depression, and many depressive patients show some anxiety disorder. PD especially is a frequently met diagnosis, as well as GAD or social phobia (Sanderson et al., 1990; Davies et al., 1995). The reported frequency, however, varies with methodology, definitional criteria used and patient population (recruitment bias, Starcevic et al., 1992). Some (epidemiological) studies have followed a large non-selected group (e.g. the Epidemiologic Catchment Area (ECA) Study of the National Institute for Mental Health (NIMH)), other researchers recruit their patients by advertisement, while others purely use the patient group referred to their clinic by other physicians. It is not surprising

that the outcome of these different studies is not unequivocal. Apart from differences as mentioned before some studies use strict criteria to include only major depression, others also include minor depression and dysthymia, some do not mention their criteria. Another point of confusion is caused by temporal/chronological issues (Moras and Barlow, 1992), as some researchers take both past and present depressive or anxiety symptoms into account, others mention a period of within two years from admission, while others investigate lifetime prevalence or just actual symptoms. In short, it is not easy to compare the results of these studies. We will briefly review the most representative studies since the late 1980s to get an impression of the frequency of comorbidity between anxiety and depression. We will keep in mind that some contrasting results may be attributable to the aforementioned methodological differences. Because most of the literature pertains to the comorbidity between panic and depression we will restrict our further analysis to PD.

Epidemiological data

In recent years there have been some reports on (some still ongoing) large epidemiologic studies, based on community samples. Examples are the Epidemiologic Catchment Area (ECA) study and the National Comorbidity Survey (NCS) in the USA, the Zurich Cohort Study in Switzerland and the Munich Follow-up Study in Germany.

The ECA study reports a lifetime prevalence for PD of 2%, the NCS of 3.5% (Eaton & Keyl, 1995). On the basis of the same ECA database Chen and Dilsaver (1995) report for PD a lifetime prevalence of 20.8% in patients with bipolar disorder of 10.0% for subjects with unipolar depression and for comparison subjects only 0.8%. Andrade et al. (1994) also analyzed a subset of the ECA-files and found a lifetime prevalence of 4% for major depression and 4% for PD: 2.1% had both, which is 11 times higher than expected by chance if both disorders were unrelated. They further analyzed this comorbid group, and found that 38% had a concomitant onset, 33.5% experienced the PD first, while in 28.5% depression preceded the PD.

Eaton et al. (1994) describe some findings from the NCS. One reason for a higher prevalence rate could be the smaller age range in the NCS (15-54 years) as compared with the ECA (18 years and older).

The results from the Munich Follow-up Study (Wittchen et al., 1993) show that between 32% and 50% of PD patients also fulfilled criteria for lifetime major depression.

The Zurich Study (Vollrath and Angst, 1989) report a 12% comorbidity at cross-section, but do not mention lifetime figures, which is not surprising because their cohort is a young adult age group.

Data from family studies

From the 1980s on several family studies have been done to investigate the possible genetic liability or clustering in families of depressive and anxiety disorders. More recently Weissman, for example, published a review of genetic studies on this subject (1993), as well as a report on their own data (Weissman et al., 1993). The results of the six reviewed studies clearly indicate the importance of genetics in PD, though morbidity risks vary from 7.7 to 20.5 in 100 probands. These figures are definitely higher than the overall prevalence rate for PD in the normal population (1.2 - 2.4 in 100). Results from the only twin study published thus far also strongly support genetic influences as monozygotic twins had five times more frequent PD than dizygotic twins, but this study has some methodological shortcomings (Weissman, 1993).

Family studies on the association between anxiety disorder and depression offer contradictory results, however. Weissman et al. (1993) found elevated rates of PD in relatives of probands with PD with or without major depression but not in relatives of probands with major depression without PD. Conversely, Maier et al. (1993) found elevated rates of major depression in relatives of probands with major depression with or without PD but not in relatives of probands with PD without major depression. The authors concluded that PD and major depression are separate disorders which are independently and specifically transmitted, while the comorbid condition does not represent a single, distinct syndrome.

Other studies cited by Weissman (1993) seem to find a higher prevalence only of secondary depression in relatives of PD patients, not of primary depression, thus supporting the separation of depression and PD. The only conclusion Weissman can suggest is that PD is highly familial, and no conclusion can be drawn yet about the comorbid condition.

Also data reviewed by Leckman et al. (1990) showed no increased risk for primary depression in PD relatives, but clearly higher risks for secondary depression.

Clinical data

In recent decades various publications have appeared that investigate the comorbidity of depression and anxiety in clinical samples. They differ amongst others in selection procedures and criteria and in methodological aspects. Some only address cross-sectional aspects, while others apply to lifetime comorbidity. There are some purely descriptive studies, whereas others relate more to treatment issues. We will review some of the results of the most recent studies on this subject.

Wetzler et al. (1995) reviewed some studies and found that 24% (range 7%-61%) of PD patients have a comorbid depressive disorder, with dysthymia more common than major depression. For lifetime prevalences the figures

increase considerably to 63%-68%. Of the patients with primary depressive disorders about 14% (range 9%-69%) have a comorbid PD. Lifetime rates were not given for this second group. Wetzler et al. state that all studies confirm that PD patients with comorbid depressive disorder have a worse course and symptomatology, but that it is not clear whether the comorbidity adversely affects response to pharmacological treatment.

In using the life-chart approach, Hunt and Andrews (1995) investigated 100 patients with anxiety disorder and could trace that in 61% the anxiety disorder preceded the major depression, and in 26% both disorders were concomitant and co-occurred independently. Their method consists of a fully structured and comprehensive diagnostic interview. The life chart is clearly a valuable progress compared with the questionable reliability of retrospective reports, and can offer a better insight into aetiological aspects on the comorbidity issue in psychiatry in general, and into the relationship of anxiety and affective disorders in particular.

Ball et al. (1995) report on 64 PD patients, most of them recruited by media-advertisement for pharmacological treatment. They were diagnosed by using the Structured Clinical Interview for DSM (SCID) or Anxiety Disorders Interview Schedule (ADIS). Of these 64 patients 48% met criteria for past major depressive episode, as 36% were in a current depressive episode. Beside these diagnoses, it was found that 60.9% of the PD patients show two or more clinically significant depressive symptoms not meeting full criteria to assign the diagnosis of depression. This illustrates the high rate of clinically significant depressive symptoms at a subdiagnostic level.

Albus and Scheibe (1993) and Albus et al. (1995) performed a two- to five-years follow-up study on 50 PD patients who were included in a clinical medication trial, and found 40% of them to be depressive as well at referral. They recruited their subjects by media announcement and included them if meeting DSM-III-R criteria for PD with or without agoraphobia. For assessment the SCID was administered, the Phobia Scale, the Hamilton Anxiety Scale and Hamilton Depression Scale and the Global Assessment Scale. They report that depressed panic patients do show a poorer outcome on overall measures on depression and anxiety, but there was no difference on measures concerning specific PD items such as frequency of panic attacks, agoraphobia and anticipatory anxiety.

In a large sample Keller et al. (1994) describe a follow-up study of 309 subjects with PD and mention 25% of them suffering from major depression at intake. They performed a prospective, longitudinal naturalistic study on a large cohort of anxiety disorder patients, part of the Harvard-Brown Anxiety Disorders Research Project. However, they do not report explicitly on depression at follow-up.

Reich et al. (1993) investigated 182 patients with PD, of whom 21% were in a current depressive episode and 50% had a lifetime major depression (past and/or current). They also state that there was no evidence that the major depressive disorder tended to be secondary to the PD, as its onset was almost equally likely to predate or postdate the first panic.

Starcevic et al. (1992) describe 54 PD patients with or without agoraphobia and report an overall comorbidity (current or lifetime) of dysthymia or depression of 61%. The instruments used in this study were the SCID and Symptom Check List 90 (SCL-90). The findings suggest that the pattern of comorbidity may differ between PD with agoraphobia, and uncomplicated PD.

Lesser et al. (1988) report on the results of the Cross-National Collaborative Panic Study, which comprises eight sites and 481 subjects (aged 18 - 65 years) who were recruited by advertisement and from clinical populations. Subjects were included if meeting DSM-III criteria for PD with or without agoraphobia, but were explicitly excluded if they had a current or past history of major depression which clearly preceded the PD. Still, 31% of the subjects showed a secondary depression after the onset of the anxiety disorder. Rating-instruments were: Hamilton Anxiety Scale, Hamilton Depression Scale, Symptom Check List 90 and the Marks-Sheehan Phobia Scale. The treatment part consisted of an eight-week, double-blind, flexible-dose study of alprazolam versus placebo. Results show that the presence of a major depressive episode did not affect treatment outcome for the panic and phobic symptoms.

Swinson and Kuch (1990) describe a series of 60 patients with PD of whom 31 (52%), by using SCID interviews, reported a history of major depressive episode. Of these 31, 40% had the onset of depression before panic, 20% concurrently, and the other 40% after the start of the PD.

From a large clinical study by Mezzich et al. (1990) a figure of 12% arises, for anxiety disorder patients also suffering from a major depression. They report on 4141 new patients presenting for care at their 24-hour a day walk-in clinic for psychiatry in Pittsburgh. They used a standardized evaluation instrument, the Initial Evaluation Form (IEF), according to DSM-III guidelines.

Di Nardo and Barlow (1990) report on their clinical sample of 292 anxiety disorder patients, referred to their specialized center for stress and anxiety disorders. Of these, 4.1% had an additional diagnosis of major depression, 11.3% of dysthymia. Of the 86 PD patients, the percentages were 6% and 12% respectively. If not only concurrent diagnoses but also lifetime figures were considered, the picture changed to a 30% of past major depressive episodes. The authors attribute their low comorbidity figures to the very specialized nature of their anxiety clinic.

As far as treatment is concerned, we have already reported that Lesser et al. (1988, 1990) failed to find any influence of comorbid depression on treatment outcome. On the contrary, Noyes et al. (1990, 1993), and Basoglu et al. (1994)

find a worse outcome for the comorbid depressive panic patients. Rosenberg et al. (1991a) reported a weak effect of comorbid concurrent depression on the outcome of PD. Except for a small group of PD patients with recurrent major depression in the past, Maddock et al. (1993) found no overall differences in treatment outcome between PD patients with one major depressive episode (primary or secondary) in their history. These authors suggest, however, that patients with recurrent major depressions represent a more serious condition.

In a review on treatment aspects of coexisting PD and major depression Laberge et al. (1992) state that comorbid depression might complicate and obstruct behavioral therapeutic (exposure) strategies for PD, but not the psychopharmacological approach, at least if sufficient attention is paid to the therapeutic compliance of the depressed panic patients.

Pollack et al. (1994) investigated a group of depressive PD patients, and found that within this group the severity of anxiety pathology was predictive of outcome. Indeed most authors agree that the presence of depressive symptoms does reflect a more severe illness condition than PD without depression.

Some authors state that more severe anxiety at baseline or longer duration of illness are negative predictors concerning treatment effect (Black et al., 1994; Katschnig et al., 1995).

Pasnau and Bystritsky (1994) report on the Harvard Anxiety-Panic Disorder Research Project which shows that PD patients who suffer from a comorbid depression have poorer treatment outcomes than either non-comorbid group.

Finally, Lydiard (1991) cites several clinical studies which show less favorable treatment outcome for comorbid conditions.

Two main conclusions can be drawn following this brief overview. The first refers to our word of caution at the beginning of this review: there is a wide variety of different approaches across the studies. Studies range from large-scale epidemiological surveys in the general population, with lay interviewers using structured instruments, to detailed analyses of small patient samples by clinicians during the course of drug trials. Strikingly, the second conclusion is that some results do emerge with a surprising good consistency. Except for two (Lesser et al., 1988 and Di Nardo and Barlow, 1990), all clinical studies agree by showing that 1:2 to 1:3 of PD patients have a lifetime diagnosis of major depression. It is suggested that amongst those who have lifetime comorbidity, half have primary depression, and half primary PD. In 1:4 to 1:5 of cases, the onset is co-occurring panic and depression. These results are supported by findings in epidemiological surveys. Cross-sectionally, most clinical studies report that 1:3 to 1:5 of the subjects with PD have concurrent depression although figures vary from a high 40% (Albus and Scheibe, 1993) to a low 12% (Mezzich et al., 1990).

While most authors suggest that comorbid depression points to a more severe condition, it is less clear whether this comorbidity affects treatment outcome.

At least three studies (Lesser et al., 1988; Maddock et al., 1993; Rosenberg et al., 1991b) found no, or only weak effects of depression on treatment results but a majority of reports state that comorbid conditions have a poorer outcome.

As we announced in the introduction of this chapter, the above figures largely confirm Breier et al.'s (1984) early findings. There is now sufficient evidence that more than half of the subjects with a PD also have a lifetime diagnosis of depression, and that depressive episodes may precede, follow or co-occur with the very first panic episode. Beyond epidemiological figures, the question of the relationship between panic and depression remains, however, unsolved. Frances et al. (1992) propose a number of possibilities, of which three are basically pertinent to our data. First, the association may exist just by chance, as both disorders may be independent diseases, which due to their respective high rate of prevalence have statistically an increased probability of co-occurring in one individual. Second, one disease may predispose to the other. Third, anxiety and depression may be two surface manifestations of one single underlying disease. A purely fortuitous association as proposed in the first model seems less likely. It is hard to believe that the high base rates of both disorders may fully account for the above figures. The third model cannot be discussed as long as our insight in the pathogeny of both panic and depression remains fragmentary. The predispositional model may suggest interesting hypotheses for further clinical investigations. Although most investigations suggest that in PD, the frequency of primary and secondary depression is equal, at least one recent report (Hunt and Andrews, 1995) found that in a majority of cases depression was secondary to panic. Most authors, as pointed out above, consider that comorbid depression may indicate a worse course of the anxiety disorder. Moreover, clinicians commonly view depression following anxiety states as a demoralization reaction. Breier et al. (1984) also noted that in the case of comorbid depression the history of the PD was longer, and the impairment worse. These issues regarding the clinical relationship between panic and depression suggested the study which will now be reported.

THE LINK BETWEEN PANIC AND DEPRESSION: A CLINICAL APPROACH

Hypotheses

While half to two thirds of PD patients have a lifetime comorbid depression, the reverse is less frequent: only 10 - 30% of mood disorder patients have a lifetime PD (Chen and Dilsaver, 1995). It has therefore been hypothesized that anxiety may predispose to depression (Frances et al., 1992). If (long standing) anxiety predisposes to depression, it will be expected that the probability for a PD patient to become depressed will depend upon the duration and severity of the PD. If depression is a consequence of panic, either via psychological

mechanisms (demoralization), or via sensitization of neuronal pathways (e.g. downregulation of receptors), it may be expected that patients with comorbid depression will benefit less from a standard treatment than uncomplicated PD subjects. As appears from the above overview, there has been suggestive evidence for several of the above hypotheses. The present study was undertaken to document the frequency of depressive pathology amongst a population of severe PD patients and to confront the above evidence on a causal link between PD and depression. The hypotheses under examination were that among PD patients referred for treatment:

- (1) as a group, patients with comorbid depression are older than nondepressed subjects;
- (2) patients with comorbid depression will have a more severe anxiety symptomatology than nondepressed subjects, as measured by standardized rating scales;
- (3) in depressed PD patients, a correlation can be found between the severity of the depressive and the anxiety symptomatology, as appears from standardized instruments;
- (4) patients with comorbid depression will benefit less from a standard treatment package, combining antidepressant drugs and behavior therapy.

Methods

The design of the study consists of a retrospective file analysis of 160 consecutive PD patients who had been referred for treatment at the Academic Anxiety Center of Maastricht from 1993 to 1995. All patients had undergone an extensive diagnostic procedure, comprising a psychiatric examination, a physical check up, and a battery of clinical metrology to assess the symptomatology, with both observer-rated and selfrating instruments.

All patients had been diagnosed on the basis of consensus by 2 experienced clinicians, using DSM-III-R criteria.

Anxiety symptoms were assessed as follows:

- The Clinical Anxiety Scale CAS (Snaith et al., 1982)
- The Selfrating Anxiety Scale SAS (Zung, 1971)
- The State Trait Anxiety Inventory, state form STAI (Spielberger et al., 1977)
- The Fear Questionnaire FQ (Marks and Mathews, 1979). We used the total score (FQT) reflecting all types of phobic avoidance as well as the specific subscore for agoraphobia (FQA).

Depressive symptomatology was assessed using the Montgomery-Asberg Depression Rating Scale MADRS (Montgomery and Asberg, 1979) and Zungs Selfrating Depression Scale SDS (Zung, 1965). Finally, patients were evaluated on the Clinical Global Impression scale (CGI).

After diagnosis, patients entered a standardized treatment procedure. This treatment comprised the administration of a specific serotonin reuptake

inhibitor (SSRI) at a clinically effective dosage for six weeks, with a complementary standardized exposure treatment from the seventh week on. This protocolled behavioral therapy was designed to last five weeks but the total duration was very flexible, depending on patients' progress. Discharge took place by mutual agreement between patient, behavior therapist and psychiatrist. At discharge all initial assessments were repeated.

Results

The data of 160 patients with DSM-III-R diagnosis of PD (and agoraphobia) were suitable for analysis. Of these 104 (65%) were female and 56 were male. Their mean age was 39 years (range: 18 - 74 years).

Forty-eight (30%) of these 160 panic patients also met DSM-III-R criteria for major depression or dysthymia. Only concurrent diagnoses of depression were accounted for, as the questionable reliability of retrospective lifetime figures for past depressive episodes does not justify strong conclusions.

The sex distribution was equally on both conditions. The mean age for the depressive subgroup was 41.8 ($\pm$ 12.5) years, mean age for nondepressed panic patients was 38.0 ($\pm$ 9.7) years, which is a statistically significant difference, $p = .042$. This finding supports our first hypothesis.

The second hypothesis on symptom-severity was tested by comparing the mean scores on the various instruments at intake for the depressed and nondepressed subgroups (Table 1). We performed a Students' T-test for unrelated samples, and two-tailed significance levels. As shown in Table 1, all measures are statistically significantly higher for the depressed panic patients, although a look at the rough mean scores justifies a question about the clinical significance of a difference between, for example 26.6 and 21.3 on the FQA, and even more so the meaning of a 0.2 difference on the CGI. We will return to this issue below.

Table 1. Mean scores ($\pm$ SD) in PD patients with (N=48) and without (N=112) depression on clinical metrology scales at baseline

	<i>Depressed PD</i>	<i>Nondepressed PD</i>	<i>p</i>
<i>MADRS</i>	15.3 ($\pm$ 8.8)	8.5 ($\pm$ 6.8)	<0.001
<i>SDS</i>	53.7 ($\pm$ 8.5)	46.2 ($\pm$ 8.5)	<0.001
<i>CAS</i>	10.6 ($\pm$ 5.9)	8.3 ($\pm$ 5.1)	0.02
<i>SAS</i>	51.2 ($\pm$ 8.1)	47.4 ($\pm$ 8.2)	0.01
<i>STAI</i>	55.4 ($\pm$ 11.3)	50.9 ($\pm$ 11.3)	0.02
<i>FQT</i>	59.7 ($\pm$ 24.2)	49.7 ($\pm$ 24.8)	0.02
<i>FQA</i>	26.6 ($\pm$ 12.2)	21.3 ($\pm$ 12.5)	0.01
<i>CGI</i>	4.9 ($\pm$ 0.5)	4.7 ($\pm$ 0.5)	0.02

The third hypothesis on the relationship between severity on depressive and anxiety measures was tested by calculating the correlation between the scores at intake on the MADRS and STAI, SAS, CAS, FQA and FQT. The Pearson correlation coefficient respectively showed to be 0.34, 0.43, 0.60, 0.18 and 0.27, all significant ($p<0.05$) (Table 2). Correlations between scores on SDS and the anxiety-scales are also shown, all of them were significant ($p<0.05$).

Table 2. Correlations between scores on Depression and Anxiety scales in PD patients with and without depression (N=160)

	<i>MADRS</i>	<i>SDS</i>
<i>CAS</i>	0.60	0.46
<i>SAS</i>	0.43	0.67
<i>STAI</i>	0.34	0.55
<i>FQT</i>	0.27	0.38
<i>FQA</i>	0.18	0.34

The fourth hypothesis, addressing the treatment-aspects, was tested by means of comparing the decrease in scores on the various questionnaires between the depressive and nondepressive subgroup (T-test for unrelated samples). Results are shown in table 3. As can be seen, both groups improve rather comparably on treatment. On the FQA the depressed group even improves more than the nondepressed.

We also compared the treatment period for each subgroup, and found the mean to be 21.3 ($\pm$ 13.4) weeks for the depressed, and 22.7 ($\pm$ 12.6) weeks for the nondepressed.

Table 3. Mean decrease ($\pm$ SD) on clinical metrology scales in PD patients with (N=48) and without (N=112) depression on clinical metrology scales at baseline

	<i>Depressed PD</i>	<i>Nondepressed PD</i>	<i>p</i>
<i>MADRS</i>	9.6 ($\pm$ 7.3)	5.3 ($\pm$ 3.6)	0.001
<i>SDS</i>	12.0 ($\pm$ 10.2)	11.1 ($\pm$ 10.4)	0.6 (NS)
<i>CAS</i>	5.9 ($\pm$ 4.0)	5.3 ($\pm$ 5.5)	0.59 (NS)
<i>SAS</i>	12.1 ($\pm$ 10.1)	12.3 ($\pm$ 10.9)	0.87 (NS)
<i>STAI</i>	14.9 ($\pm$ 13.5)	16.6 ($\pm$ 13.9)	0.49 (NS)
<i>FQT</i>	33.3 ($\pm$ 23.4)	27.8 ($\pm$ 23.1)	0.17 (NS)
<i>FQA</i>	18.6 ($\pm$ 12.1)	14.0 ($\pm$ 12.9)	0.04
<i>CGI</i>	5.9 ($\pm$ 4.0)	2.2 ($\pm$ 1.1)	0.92 (NS)

Conclusion

The results of our own study corroborate existing data on the high prevalence of depressive disorders in patients with PD. In our sample 48 out of 160 PD patients presenting for treatment had concurrent depression. This rate of 30% compares to the overall 1/5 to 1/3 rate of cross-sectional comorbidity reported in the literature we have reviewed. In our calculation we did not take into account the distinction between major depression and dysthymic disorder which was in force in the DSM III-R. Had we done so, the figure of comorbidity with major depression alone had been lower by about 50% which still compares with the 12% of major depression found by Mezzich et al. (1990) or the 21% by Reich et al. (1993).

Some have argued that the high comorbidity of anxiety and depression found in clinical samples is in fact related to a recruitment bias, because patients with a comorbid depression are more prone to seek treatment than those without comorbidity. However, general population surveys have shown comparable high rates of comorbidity (Wittchen and Essau, 1993).

Thus, it seems that the present study adds some evidence to the existing data on a high cross-sectional depressive comorbidity in clinical samples of patients with a PD.

Three hypotheses addressed the possible causal relationship between PD and depression. We had predicted that PD patients with depression would be older than those without depression. If the existence of a PD predisposes to depression, either via psychological or biological mechanisms, it is perfectly credible that the longer the anxiety disorder exists, the higher the probability that a depressive episode appears. The age of onset of PD is normally distributed around a peak of 25 years, comorbid depressive episodes will tend to be more frequent in older patients. The findings are in line with our prediction: we found significant differences, between depressives and non depressives, the former being indeed older.

We had predicted that as a group, PD patients with depression would have a more severe anxiety symptomatology than those without depression. If there is a causal relationship between PD and depression, the more severe the former, the more probable the latter. Again, the results substantiated our hypothesis. On all measures, the anxiety scales consistently showed more severe symptomatology in depressives compared with non depressives. This observation is in line with several other reports cited above, repeatedly suggesting that the global clinical condition of comorbid patients is worse compared with non-complicated panic.

If anxiety causes depression, the more severe the former, the more severe the latter. We had predicted that at an individual level there should be a correlation between the severity of the anxiety disorder and the severity of depressive symptoms. Again, our findings were in line with the expectations. All

correlations between scales for anxiety and scales for depression were statistically significant.

As far as the two latter predictions are concerned, some cautionary remarks must be made. We used standardized instruments, and all clinical metrology was done by an independent rater, who, at least at baseline, was blind to the diagnosis of the patient. However, there is a notorious item overlap between anxiety and depression scales (Snaith, 1993), which is responsible for a serious contamination between the measurement of anxiety and depressive symptoms. This factor may account in part for our findings. Yet, no item overlap with depression scales apply to the FQ, which is a specific instrument designed to measure behavioral avoidance, in particular agoraphobia.

There was an overall positive treatment effect, as shown by Table 4.

Table 4. Mean scores ($\pm$ SD) on clinical metrology scales post treatment, by depression

	<i>Depressed PD</i>	<i>Nondepressed PD</i>	<i>p</i>
<i>MADRS</i>	5.6 ($\pm$ 4.0)	2.8 ($\pm$ 4.0)	0.001
<i>SDS</i>	41.7 ($\pm$ 8.9)	34.7 ($\pm$ 10.2)	<0.001
<i>CAS</i>	4.8 ($\pm$ 3.5)	3.1 ($\pm$ 3.7)	0.02
<i>SAS</i>	39.2 ($\pm$ 9.2)	34.9 ($\pm$ 9.9)	0.01
<i>STAI</i>	40.6 ($\pm$ 13.3)	34.2 ($\pm$ 11.6)	<0.01
<i>FQT</i>	26.4 ($\pm$ 17.3)	21.9 ($\pm$ 21.1)	0.16 (NS)
<i>FQA</i>	8.0 ($\pm$ 6.5)	7.2 ($\pm$ 8.5)	0.51 (NS)
<i>CGI</i>	2.8 ($\pm$ 1.2)	2.5 ($\pm$ 0.2)	0.25 (NS)

At discharge, there still was a significant difference on the MADRS and the SDS between both groups of patients. The same applies to the 'general' scales of anxiety (CAS, SAS, STAI). However, it should be noted that the ratings of the former depressives were well below any clinically significant threshold on the MADRS, as well as on the SDS. Most importantly, in contrast to the baseline measurement, any between-group difference had disappeared on the sole specific anxiety rating represented by the FQT and FQA variables.

In line with a number of previous reports, we had expected that a PD patient with a comorbid depression would benefit less from treatment than the PD patients without depression. We failed to find empirical support for this hypothesis. The results firmly contradicted our prediction. No single rating suggested that the group of depressives had poorer results than the nondepressives. On the contrary, if anything there was a difference in favour of the patients with depression, who displayed a greater decrease on the agoraphobia subscale of the FQ. This may relate to the higher initial value of the depressive group on this variable (law of initial values, cited by Woodman et al., 1994). The resolution of the depressive disorder and the related improvement in activity may have influenced this variable as well. No argument

was found to suggest that PD patients who are depressed will have less benefit from treatment than other PD patients. We calculated the mean time in treatment for both groups, knowing that the time of discharge had been determined in mutual agreement between clinicians and patient, based on the overall clinical condition. For this parameter we failed to find any difference between depressives and non depressives. Our results are consistent with a number of recently published studies (Albus et al., 1995; Brown et al., 1995).

The results of the present retrospective study are a good illustration of the state of affairs as far as the comorbidity between anxiety and depression is concerned. The caveats which have been formulated at the beginning of this chapter apply. We accept the current diagnostic systems in use (DSM III, III-R and IV, and ICD-10) as working hypotheses. In these systems, anxiety (e.g. PD) and depression are presented as separate entities. However, there is plenty of evidence that both disorders are strongly interrelated.

Returning to the three models we have discussed:

- (1) - association by chance of two diseases with a high base rate of prevalence;
- (2) - one disease predisposing to another;
- (3) - two surface manifestations of one underlying process;

We have found, in the recent literature as well as in the above study, a number of arguments in favour of the second theory. In spite of some reservations due to the retrospective nature of the design, our data support this idea that PD may cause depression. It is worth noting that the reverse may not be true: only a minority of depressive patient seems to develop PD (Chen and Dilsaver, 1995). If this holds true it may be an argument against the third model. A one-way causal relationship is not compatible with merely one single underlying disease. Arguments in favor of one or two diseases are not likely. It seems more likely that as long as the understanding of the pathogenic mechanisms of PD and depression are not fully understood, and matched with the classification systems, the issue of comorbidity will not be solved.

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4. COMORBIDITY OF OBSESSIVE COMPULSIVE DISORDER AND DEPRESSION: PREVALENCE, SYMPTOM SEVERITY, AND TREATMENT EFFECT

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ABSTRACT

Background: The goal of this study was to investigate the co-occurrence of depressive disorders in obsessive-compulsive disorder (OCD) and the effect of these disorders on combined pharmacologic and behavioral treatment for OCD.

Method: A retrospective chart analysis was performed on baseline ratings of 120 OCD patients and posttreatment ratings of 72 of these patients. For depressive symptoms, the Montgomery-Asberg Depression Rating Scale (MADRS) and the Self-Rating Depression Scale (SDS) were applied, for obsessive-compulsive symptoms the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Maudsley Obsessive Compulsive Inventory (MOCI) were used; and for general anxiety symptoms, the Self-rating Anxiety Scale (SAS), the Clinical Anxiety Scale (CAS) and the State-Trait Anxiety Inventory (STAI-1) were given.

Results: One third of the OCD patients in our sample were found to be depressed. Symptom severity on OCD symptoms at baseline did not differ between depressed and nondepressed OCD patients; on general anxiety symptoms, the comorbid group was more severely affected. Both depressed and nondepressed OCD patients responded well to treatment, as reflected in assessments for depressive, obsessive-compulsive and general anxiety symptoms. However, comorbid depression had a negative effect on treatment: depressed OCD patients showed less improvement than nondepressed OCD patients on most scales.

Conclusion: Depression frequently accompanies OCD and appears to affect treatment outcome negatively. While both groups of patients improved with combination treatment the OCD-alone group had more improvement than the group that had comorbid depression.

INTRODUCTION

Clinical psychiatric conditions frequently show overlap between different psychopathologies. Clinical studies have demonstrated that different diagnoses may coexist. A large number of epidemiological studies have shown a relationship between anxiety disorders and affective disorders (Angst, 1996; Regier et al., 1998). Since several studies report that over 90% of individuals with anxiety disorders have a lifetime history of other psychiatric problems, anxiety disorders rarely exist in isolation (Kaufman and Charney, 2000). Comorbidity of any of the anxiety disorders with depression is also very common: panic disorder (PD) with or without agoraphobia, social phobia (SP), generalized anxiety disorder (GAD) and obsessive compulsive disorder (OCD) display a higher than expected rate of co-occurrence with depressive disorders (Sanderson et al., 1990; Wittchen et al., 1999). These studies contribute to speculations about etiology, pathophysiology, psychopharmacology, and behavioral treatment. In the present study, we report on the comorbidity of OCD and depression in an outpatient population that was referred for treatment of OCD.

The magnitude of the comorbidity reported in the literature varies widely (Angst, 1996) and depends on methodology (study design and experience of interviewers), samples (community or treatment), and case definition (diagnostic criteria and thresholds). The term comorbidity should be used with caution and should be properly defined. However, in various studies, its use is often vague or erroneous. Maser and Cloninger (1990) mention the large number of definitions that are commonly used. Ideally, comorbidity should be restricted to disorders and syndromes but is, in effect, also used to describe the co-occurrence of symptoms. Another erroneous use derives from the nature of the current classification system in psychiatry. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, APA, 1994), is intentionally designed to serve as a taxonomic instrument and therefore offers criteria for inclusion and exclusion, but pathognomonic signs in psychiatry are lacking and a diagnosis is cumulatively made based on the presence of clusters of symptoms. Another confusing factor is the chronological appearance of diseases, since comorbidity can be present throughout a patient's lifetime, at any time in the past, or just at the moment that another disorder exists. Because of the absence of a theoretical basis in the classification system, careful use of DSM-IV is warranted in cases of comorbidity.

The coexistence of more than one psychiatric disorder at a time can also have both theoretical and practical implications. For example, theoretically, the high co-occurrence of more than one psychiatric disease may suggest shared pathogenic or genetic factors. If chronological patterns occur at the same time,

certain causal links may be established or preventive action taken. Furthermore, practical clinical implications could be that course and response to treatment differ between patients with one or more diagnoses. For example, it has often been suggested that depressed PD patients are more resistant to treatment than patients with PD alone (Noyes et al., 1990).

To interpret prevalence rates of comorbid disorders, individual prevalence rates are needed. For OCD these figures have gradually grown over the years. For a long time, OCD was thought to be quite rare since people are apparently reluctant to request treatment due to fear or shame (Rasmussen and Eisen, 1992). Recent epidemiological studies have shown a six-month prevalence rate of OCD of approximately 1% (Bebbington, 1998) and a lifetime prevalence rate of 2% to 3% (Hollander, 1997; Regier et al., 1998; Sasson et al., 1997; Weissman et al., 1994), which implies that OCD is much more common than formerly suggested. The lifetime prevalence rate for depressive disorders varies from about 8% (Regier et al., 1990) to 11.7% (Wittchen et al., 1999).

As reported in several studies (Black and Noyes, 1990), depression is the most frequent complication of OCD. Comorbidity rates in reported studies vary widely, from 19% to 90% (Milanfranchi et al., 1995). This is largely due to methodological and semantic differences. Within this wide range, however, most epidemiological studies show that about one third of OCD patients suffer from a lifetime depressive episode. In clinical populations comorbidity rates are increasing to about two thirds (Crino and Andrews, 1996). Rasmussen and Eisen (1992) found that one third of OCD patients suffer from concurrent depression at referral and two thirds suffer from lifetime depression. A possible explanation for the discrepancy between clinical and nonclinical studies may be that many OCD patients only seek help when depressed, as suggested by Black and Noyes (1990). As for chronology, it is reported that most often the onset of OCD is before that of depression (38%), whereas transition from depression to OCD occurs in only 11% of cases (Black and Noyes, 1990).

As noted earlier, the therapeutic implications of a comorbid depressive disorder in OCD are still poorly understood. Comorbidity affects the outcome of behavioral versus pharmacotherapeutic interventions. For example, in OCD, severe depression may worsen the prognosis for behavioral treatments, whereas most studies suggest that pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs) is equally effective for OCD with or without concomitant depression (Den Boer, 1997).

To better understand the previously mentioned wide range of reported comorbidity, to appreciate the limitations of these studies, and to gain insight into questions regarding the impact of treatment, we decided to conduct the following study in our clinical sample of OCD patients. We investigated the prevalence of depressive disorder as a comorbid diagnosis in a sample of OCD patients in our outpatient clinic, which specializes in anxiety disorders.

Comorbidity was defined as the coexistence of two syndromes (i.e., OCD and depressive disorder according to the DSM-IV criteria, not only the presence of sub-syndromal symptoms). We also sought to assess the influence of a comorbid depression on treatment outcome for OCD.

Hypotheses were posed as follows: (1) as reported in other studies, point prevalence of depressive disorder in OCD will be in the range of 30% to 60%; (2) the presence of a comorbid depression will be reflected in more severe symptoms of OCD and, therefore, in higher scores on the Maudsley Obsessive Compulsive Inventory (MOCI) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS); and (3) the effect of combined psychopharmacologic and behavioral treatment for OCD will not differ between depressed and nondepressed OCD patients.

MATERIALS AND METHODS

We performed a retrospective chart analysis. One hundred twenty patients with DSM-IV axis I OCD as their principal diagnosis were included for baseline (prevalence and severity) assessments; for 72 patients, posttreatment data were also available. Patients were referred for treatment to the Academic Anxiety Center Maastricht, the Netherlands, from 1995 through 1999. As part of a standard protocol, all patients were evaluated by means of a semi-structured psychiatric interview, with special emphasis on anxiety and affective spectrum symptoms. A diagnosis was made according to DSM-IV criteria and confirmed by two experienced psychiatrists. Patients also received a physical examination and were additionally evaluated by means of the following standardized questionnaires and structured interviews: The Yale-Brown Obsessive Compulsive Symptoms (Y-BOCS, Goodman et al. 1989); the self-rating Maudsley Obsessive Compulsive Inventory (MOCI, Hodgson and Rachman, 1977); the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979); the Self-Rating Depression Scale (SDS, Zung, 1965); the Clinical Anxiety Scale (CAS, Snaith, 1982); the Self-Rating Anxiety Scale (SAS, Zung, 1971); and the State Trait Anxiety Inventory, state form (STAI-1, Spielberger, 1977).

Patients were offered combined psychopharmacological and behavioral therapy after the diagnostic procedure was completed. Initially, in the first phase, patients received pharmacotherapy, i.e., a prescription for one of the current SSRIs, in increasing dosages for 10 to 12 weeks (up to effective clinical doses or maximum doses of 300 mg of fluvoxamine, 60 mg of fluoxetine, or 60 mg of paroxetine), with a visit for a global clinical assessment at our clinic every 2 to 4 weeks. In the second phase, behavior therapy was added, based on exposure and response-prevention intervention. The duration of the two phases was flexible, depending on individual clinical progression. For example,

some OCD patients benefited from medication to such an extent that only a few sessions of behavior therapy were needed to stabilize the symptoms and to obtain satisfactory results, whereas other patients were more complicated in the sense that they needed more prolonged and sometimes extensive behavioral therapy. Discharge was planned by mutual agreement between patient, behavioral therapist, and psychiatrist. At discharge, the initial psychopathological rating scales were repeated (posttreatment assessments).

Subjects

The data of 120 consecutive OCD patients referred to our center from 1995 to 1999 were included in the study for baseline ratings. For 72 patients, posttreatment assessments were also available. Data from this group were analyzed for treatment effect. Patients were included if a diagnosis of OCD was made as the principal diagnosis on DSM-IV axis I. Because of the nature of our clinic, even in comorbid cases, the reason for referral was the OCD. The exclusion criterion for the present study was missing data at baseline.

Analysis

All statistics were performed with Statistical Package for the Social Sciences (SPSS-PC), version 10. Students' T-test for independent samples was used to test differences between depressed and nondepressed OCD subgroups at baseline and after treatment. A T-test for paired samples was used to test differences before and after treatment for the 72 completers. A Chi-square test was applied to test the proportion of males and females having a depression. Chi-square tests were also used to compare the distribution of depressives in the group of completers and noncompleters. Hypotheses regarding improvement were analyzed using a multivariate analysis of variance (MANOVA).

RESULTS

Baseline values

Demographics. The majority of the patients in the study had been referred by their family practitioner; some had been referred by psychiatrists. Of the 120 subjects we assessed at baseline, 40 (33%) were male and 80 (67%) were female. Nineteen (40%) of the 48 patients who were assessed only at baseline were men, and 29 (60%) were women (nonsignificant [NS]). Of the 72 patients who also received a posttreatment assessment, 21 (29%) were men and 51 (71%) were female (NS).

The mean $\pm$ SD age of our 120 baseline subjects was 37.8 ± 12.1 years. The mean age of the women was 37.1 ± 11.7 years; for the men it was 39.3 ± 12.8 years (NS). The depressed patients were 37.6 ± 11.3 years of age, and the

nondepressed were 37.9 ± 12.6 years of age (NS). The mean age of the completers was 39.2 ± 14.0 years, and that of the noncompleters was 37.0 ± 10.7 years (NS).

Prevalence. To address our first hypothesis on the prevalence of a comorbid depressive disorder, all 120 patients were considered. Of these 120 baseline patients with OCD as the principal axis-I diagnosis, 44 patients (37%) also met DSM-IV criteria for depressive disorder at the time of referral (point prevalence). The distribution in the group that had only one assessment was 19 (40%) with comorbid depression and 29 (60%) without depression; in the posttreatment group, 25 patients (35%) were depressed at baseline, whereas 47 patients (65%) were not (Chi-square NS).

Notably, the gender distribution in the comorbidity subgroups, as well in the completers as in the noncompleters, was decidedly female. It appeared that (for all 120 baseline subjects) only a minority of male OCD patients suffered from comorbid depression - only 6 (15%) of 40 compared with 38 (48%) of 80 of the female OCD patients (chi-square 12.12, $p=.001$). For the 72 completers, only 2 of 21 men were depressed, versus 23 of 51 women (Chi-square 8.30, $p=.006$).

Severity. To answer the second hypothesis on symptom severity we looked at the mean scores for the 120 baseline subjects and at the subgroups of completers and noncompleters. Mean scores on baseline assessment scales are reported in Table 1. The severity of symptoms at intake for all 120 patients differed for depressed and nondepressed OCD patients only on the general anxiety (CAS $p<.001$, SAS $p=.001$, and STAI-1 $p<.001$) and depression measures (MADRS $p<.001$ and SDS $p<.001$), not for the specific OCD measurements (MOCI [NS] and Y-BOCS [NS]). The severity of initial symptoms across the subgroups completers and noncompleters only differed on the Y-BOCS ($p=.035$), with the important finding that the noncompleters showed a lower mean value. Within the group of depressed OCD patients, there were no differences on assessments between completers and noncompleters. Interestingly, however, within the nondepressed OCD patient-group it was the completers who had significantly higher scores on the Y-BOCS ($p=.017$) and MOCI ($p=.049$).

Posttreatment values

To test the third hypothesis on treatment effect, the data of the 72 completers were analyzed (Table 2). Mean treatment duration did not differ significantly between the groups: depressed OCD patients were discharged after 29 ± 9 weeks and nondepressed patients after 28 ± 13 weeks (NS). Although the mean scores on the MADRS (Figure 1) were not significantly worse for the depressed patients compared with the nondepressed patients posttreatment, on the SDS (Figure 2) the formerly depressed patients still showed significantly more severe ($p=.001$) symptoms. Posttreatment scores on the Y-BOCS ($p=.02$) (Figure 3) and MOCI ($p=.004$) (Figure 4) were worse for the depressed OCD patients, although on these scales depressed and nondepressed patients were equally affected at baseline. Also, symptoms on two of the three general anxiety measures (SAS, $p<.001$; STAI-1, $p=.004$) were worse for the depressed OCD patients (Table 2).

Treatment effect

Treatment proved to be effective on all measures (Table 2). Paired-samples T-tests showed significant lower mean scores on the posttreatment assessments ($p<.001$). The repeated-measures MANOVA also revealed significant time effect on all measures for both depressed and nondepressed OCD patients. Differences between the depressed and nondepressed groups were statistically significant for measures on the MADRS, SDS, STAI-1 and SAS, but not statistically significant on the CAS, MOCI and Y-BOCS (p -values in Table II). MANOVA tests showed a significant time-by-group interaction effect on the MADRS and the MOCI, suggesting that nondepressed patients improved significantly more than depressed ones on these scales. For the other measurements there were no significant interaction effects. Thus, on these scales, both subgroups improved to a similar extent.

Table 1. Baseline scores for Completers versus Noncompleters among patients with OCD

Scale	Completers (N=72)		Noncompleters (N=48)		Total (N=120)	
	Depr OCD	OCD	Depr OCD	OCD	Depr OCD	OCD
MA-DRS	21.0 (± 11.3)	11.9 (± 6.8)	23.0 (± 7.1)	9.5 (± 7.1)	21.9 (± 9.6)	11.0 (± 7.0)
SDS	58.2 (± 9.0)	49.9 (± 9.4)	58.2 (± 6.0)	46.4 (± 10.6)	58.2 (± 7.8)	48.6 (± 9.9)
MOCI	18.5 (± 6.9)	19.8 (± 4.9)	19.0 (± 6.3)	16.6 (± 7.2)	18.7 (± 6.6)	18.6 (± 6.0)
Y-BOCS	32.7 (± 6.6)	31.8 (± 5.8)	30.9 (± 7.1)	27.4 (± 7.0)	31.8 (± 6.8)	30.2 (± 6.6)
ST-AI	62.3 (± 11.5)	52.8 (± 12.5)	60.5 (± 11.6)	48.7 (± 15.3)	61.5 (± 11.5)	51.2 (± 13.7)
C-4S	12.3 (± 4.6)	8.9 (± 4.8)	15.2 (± 5.9)	7.1 (± 4.9)	13.6 (± 5.4)	8.2 (± 4.9)
S-4S	49.3 (± 9.1)	45.5 (± 9.5)	51.1 (± 7.1)	41.3 (± 9.1)	50.1 (± 8.3)	43.9 (± 9.5)

Table 2. Treatment Effect in Completers (Mean ± SD)

Scale	Depressed OCD		OCD		MANOVA		
	Baseline	Posttreatment	Baseline	Posttreatment	Posttreatment p	Time p	Time by group p
MA-DRS	21.0 (± 11.3)	6.4 (± 7.8)	11.9 (± 6.8)	3.7 (± 4.4)	NS	<0.001	0.029
SDS	58.2 (± 9.0)	45.2 (± 11.1)	49.9 (± 9.4)	36.6 (± 9.4)	0.001	<0.001	NS
MOCI	18.5 (± 6.9)	13.2 (± 7.0)	19.8 (± 4.9)	8.1 (± 6.8)	0.004	<0.001	0.002
Y-BOCS	32.7 (± 6.6)	14.9 (± 10.5)	31.8 (± 5.8)	9.2 (± 6.6)	0.022	<0.001	NS
ST-AI	62.3 (± 11.5)	45.7 (± 14.9)	52.8 (± 2.5)	36.1 (± 11.8)	0.004	<0.001	NS
C-4S	12.3 (± 4.6)	5.0 (± 4.4)	8.9 (± 4.8)	4.3 (± 5.8)	NS	<0.001	NS
S-4S	49.3 (± 9.1)	40.8 (± 9.4)	45.5 (± 9.5)	32.6 (± 7.4)	<0.001	<0.001	NS

Figure 1. Mean MADRS at Baseline and Post Treatment for Depressed and Not-depressed OCD Patients. Total N=72, Depressed N=25, Not-depressed N=47

Figure 2. Mean SDS at Baseline and Post Treatment for Depressed and Not-depressed OCD Patients. Total N=72, Depressed N=25, Not-depressed N=47

Figure 3. Mean Y-BOCS at Baseline and Post Treatment for Depressed and Not-depressed OCD Patients. Total N=72, Depressed N=25, Not-depressed N=47

Figure 4. Mean MOCI at Baseline and Post Treatment for Depressed and Not-depressed OCD Patients. Total N=72, Depressed N=25, Not-depressed N=47

DISCUSSION

As for our first hypothesis, which defined comorbidity as coexistence of two separately defined psychiatric disorders according to full DSM-IV criteria, we found a point prevalence of depressive disorder of 37% in our clinical sample of OCD patients. This was well within the range we expected on the basis of earlier cited clinical studies (Black and Noyes, 1990; Perugi et al., 1997). However, it did not support the assumption that the majority of OCD patients only seek help when depressed, since 37% is not much higher than most population-based epidemiologic studies (Crino and Andrews, 1996) have reported for concurrent depression. The mean MADRS score for the total group of depressed OCD patients in the present study appeared rather low (mean 21.9, SD=9.6), reflecting depressive disorder of only moderate severity. Moderate depression would seldom be a reason to seek help since depressive symptoms are easily accepted as a rather normal reaction to impairment by OCD, whereas severe levels of depression interfere more with daily life and affect the quality of life to a greater extent.

It was interesting to find that there was a significant difference in gender among the group with comorbid depression. There were more females with comorbid OCD and depression in the ratio of 3.2:1, in our sample. This was higher than the known (epidemiological) ratio of 2:1 female:male ratio for depressive disorder alone. A higher ratio for depression in OCD has, to our knowledge, not been reported in other clinical studies before. However, this finding should be interpreted with caution. In the first place, because there are reported general differences in treatment-seeking behavior between males and females. Secondly, there are only few studies that report on gender differences in OCD in relation to depressive disorder, and in these the additional risk for females did not exceed the reported epidemiological gender distribution for depressive disorder. Female relatives of OCD patients seem to have a higher risk of developing depressive disorder (but not OCD) than male relatives (Sciuto et al., 1995). Another study by Castle et al. (1995) explicitly addressed gender differences in OCD, and found that more female OCD patients were on antidepressant medication or had a past history of treatment for a depression than male OCD patients, but the distribution was in line with the gender ratio for depression alone.

Our second hypothesis, that OCD patients with comorbid depression tend to show more severe symptomatology than nondepressed OCD patients, could not be confirmed for scores on the specific OCD rating scales Y-BOCS and MOCI. Depressed patients however did show more severe symptoms on the general anxiety scales CAS, SAS, and STAI-1. However, these scales are known

to measure not only specific symptoms of anxiety disorders but also non-specific feelings of stress and show overlap with depressive symptoms (Keedwell and Snaith, 1996). As could be expected, the specific depression assessments MADRS and SDS showed significantly higher scores for the depressed patients. So the most interesting finding regarding symptom-severity is that baseline values of the specific OCD rating scales MOCI and Y-BOCS did not differ significantly between depressed and nondepressed OCD patients. There are at least two possible explanations for this. The first possibility is that OCD and depressive disorder are two separate diagnostic entities (Delgado and Moreno, 1998) and thus no correlation between depression and OCD scales would be expected. A second explanation could be that the scores on the MOCI and Y-BOCS in our sample were quite high from the start, so there was not much room for significant variation (ceiling effect) and presumably more suffering could only be reflected in the other, more general anxiety-related, scales. In any case, with regard to symptom severity, we can conclude that comorbid, depressed OCD patients showed more severe (general) anxiety and depressive symptoms than nondepressed OCD patients, but their baseline level of OCD symptoms was the same.

As for the third hypothesis on treatment effect, we were able to confirm that both depressed and nondepressed OCD patients profit from the combined treatment offered for OCD. Both improved significantly during therapy with a reduction of more than 50% on initial scores on the MADRS, Y-BOCS and CAS. The scores on the SDS, MOCI, STAI and SAS also showed significant decreases of between 25% and 50%. It is interesting to note that the measurements which show the best improvement are investigator-rated scales, whereas the self-rating instruments show a smaller range of improvement. The phenomenon that clinician-scored measures often show more improvement than do the self-administered questionnaires has been described before (Van Balkom et al., 1994).

Although the baseline scores for the depressed subgroup did not differ on the OCD measures, after treatment the depressed OCD patients scored significantly higher on the Y-BOCS and MOCI than did the nondepressed patients, reflecting more remaining symptoms. Also, on the general self-report anxiety scales SAS and STAI-1, after treatment the depressed patients still had higher symptom severity than the nondepressed ones. This finding, that the residual scores on several scales posttreatment were higher for the depressed subgroup did point to the fact that a combined occurrence of obsessive-compulsive and affective symptoms showed more resistance to treatment or complicates treatment. Treatment duration, however, was similar in both groups. The frequent co-occurrence of depression in OCD has formerly led to hypotheses about OCD being an affective variant (Zohar and Insel, 1987). This is partly supported by the therapeutic benefit of antidepressant agents for OCD

(Picinelli et al., 1995). Initial studies mention that levels of depression at the outset are important for the final outcome (Marks, 1982). However, later meta-analytic studies have shown that the beneficial effects of antidepressants such as clomipramine and of SSRIs on OCD symptoms are unrelated to the presence of depressive symptoms (Den Boer, 1997; Picinelli et al., 1995; Mavissakalian, 1985), which again undermines this hypothesis and implies another relationship between the two disorders. Hollander et al. (1991) state that depressive symptoms interfere with the response to both psychopharmacologic and behavioral treatments of OCD. Also, Foa (1979) reported behavioral therapy outcome to be negatively influenced by the presence of (severe) depressive disorder. Montgomery (1998) argues that depression seen in OCD should be regarded as part of OCD and not as a separate disorder of major depression, for depressive symptoms in OCD can, in his view, only be expected to respond to effective antiobsessional treatments and not to noradrenergic antidepressive agents. Delgado and Moreno (1998) emphasize the different etiology and pathophysiology of OCD and depression, as implicated by tryptophan depletion studies and neuroimaging. Although there may be some shared elements or contributions of neural networks, there is no complete overlap. One may generally conclude from these pharmacologic, depletion and imaging data that, although linked, OCD and major depression are two different psychopathological entities which, if diagnosed carefully, require different therapeutic strategies. These data support the notion that it is more difficult to treat two psychiatric disorders at a time than one. This is partly confirmed by the present study, as more severe symptoms remained in the initially depressed patient group than in the nondepressed group.

Some shortcomings of this study must be mentioned. First, the nature of the study imposed restrictions on the interpretation of our findings, as retrospective studies always do. Even though, we used a semi-structured interview and DSM-IV criteria, and always required diagnostic agreement from two clinicians. Secondly, as described above, some of our rating instruments were self-rated scales and, as such they were more liable to subjective interpretation and were less reliable. Thirdly, we had at our disposal posttreatment data of only 72 of the 120 patients we examined at baseline. We were unable to trace all subjects. There are various reasons for this. Patients sometimes ended their therapy prematurely if there was no clear or rapid effect; others were doing well after treatment and did not show up for posttreatment assessments. What we do know, however, is that the demographics and clinical values at baseline did not differ between the group of completers and the patients we only assessed at baseline. Thus, they were not specifically the most depressed or severe patients who were lost to follow-up, on the contrary, for example within the non depressed subgroup the completers showed more severe symptoms at baseline assessments.

At the same time, one should see the shortcomings above in relation to the strengths of this study, which are the clear-cut definition of comorbidity and its naturalistic nature. Defining comorbidity as current, co-existing DSM-IV-defined syndromes is one of the most reliable assessments of comorbid conditions. Patients' reports of past lifetime events have never been proven to be very reliable; the only way to counter this is to do longitudinal research on large patient groups, and this design has its own drawbacks. An advantage of naturalistic studies like this is, in our opinion, that the results are directly derived from general clinical practice, and this is relevant for patients in the clinical setting. Diagnosing comorbid conditions is of great importance since they can have an impact on treatment outcome.

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Section II. Panic disorder and associated phenomena

5. SUICIDAL IDEATION IN PANIC DISORDER PATIENTS

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INTRODUCTION

The debate on suicide risk for panic disorder (PD) patients has intensified since publication of the Weissman et al. report (1989), which was based on epidemiological data from the Epidemiologic Catchment Area (ECA) study. The authors stated that PD patients have a 20% risk for suicide attempts, that 12% of people with panic attacks but not PD actually attempt suicide and that 47% of all PD patients report suicidal ideation. Because clinicians are only infrequently confronted with PD patients who express suicidal thoughts (Appleby, 1994; Noyes, 1991), these findings were quite surprising. The Weissman et al. study, however, suffered from methodological drawbacks, such as the use of lay interviewers and the nonclinical population investigated. Moreover, they only partly controlled for such lifetime comorbid disorders as substance abuse, depressive disorders, and borderline personality disorder, all of which are known to be associated with increased suicidality. Each comorbid disorder was controlled for separately (e.g. when controlling for depression, they did not control for alcohol abuse).

Subsequent studies gave contrasting results. Reanalyzing the same set of data from the ECA study and controlling only for axis I comorbid disorders, Johnson et al. (1990) still found a higher suicide risk for uncomplicated PD (7%, vs. 7.9% in major depression). King et al. (1995) showed that a lifetime prevalence of panic attacks and PD contributed substantially (almost twofold) to suicide risk in depressed patients. The results of studies by Allgulander and Lavori (1991), Anthony and Petronis (1991), Noyes (1991), and Noyes et al. (1991) are consistent with those of Weissman and colleagues. Admittedly, these studies have important methodological differences, but they do indicate an increased suicidality in PD patients. Allgulander and Lavori studied an inpatient (i.e., more severe) population, and grouped together all 'anxiety neuroses', thus, creating a more heterogeneous group. Noyes et al. did not control for comorbid disorders; they performed a 7-year follow-up study to investigate predictor variables for suicidal behavior. Very recently, Woodruff-Burden et al. (1997) studied 627 non-clinical subjects (students) and reported a relationship between panic and suicidality in a complex interaction with other general (psycho) pathology; comorbidity was not ruled out.

Another recent study (Korn et al., 1997) reported a higher rate of aggressive tendencies in comorbid depressed panic patients (both inwardly and outwardly directed) during panic attacks than in nondepressed panic patients. These authors also found a high correlation between panic-associated suicidality and aggression, and measures of impulsivity, suicide risk, and violence risk.

Several researchers could not replicate a higher suicide risk in PD. When comorbidity was ruled out, Beck et al. (1991), Griez et al. (1994), and Warshaw et al. (1995) failed to find increased suicidality. Friedman et al. (1992) and

Lepine et al. (1993) demonstrated that a higher suicide risk could be attributed completely to comorbid depressive, addictive, or (borderline) personality disorder.

Hornig and McNally (1995) also reanalyzed the original ECA data and controlled for combined lifetime comorbid disorders, whereas Weissman et al. only controlled for separate comorbid disorders. The former concluded that PD was not associated with an increased risk for suicide attempts. Cox et al. (1994) found past suicide attempts in PD patients to be related to the context of depressive symptoms, even when they did not meet the full diagnostic criteria for a major depression.

In this context, it must be noted that the studies supporting the idea of increased suicidality in PD are largely epidemiological, and to a lesser extent clinical in nature. Yet, there are several clinical studies that disaffirm this relationship.

The aim of the present study was to look for suicidality, and in particular suicidal ideation, in PD patients without any comorbid axis I or II diagnosis. It was not our intention to look prospectively for suicide risk. We did inquire about past suicide attempts in an effort to estimate the severity of any existing suicidal thoughts and, thus, of suicide risk.

METHODS

The aim of the present study was to assess suicidal ideation and a history of suicide attempts in patients presenting with uncomplicated (i.e., no comorbid DSM-III-R axis I or II pathology) PD with or without agoraphobia. It was hypothesized that patients with 'pure' PD (i.e., without comorbid affective, addictive, or personality pathology) would not be at an increased risk for suicide compared with a group of normal controls.

Subjects

Fifty patients referred for treatment to the Academic Anxiety Center in Maastricht, a tertiary outpatient clinic for anxiety disorders, voluntarily participated in the study. They were included if they met the DSM-III-R criteria (APA, 1987) for PD with ($n=40$) or without ($n=10$) agoraphobia, and without any comorbid (past or present) axis I or II diagnosis. The mean age of the 30 female and 20 male subjects was 38 years. Close attention was paid to comorbidity. After the clinical interview, another investigator reviewed all files. If there was any doubt about (lifetime) depression, personality disorder, or substance abuse, the patient was excluded from the study. Fifty age- and sex-matched controls without any psychiatric pathology were selected. All subjects were interviewed by a M.D. who presented them with four items (the same ones used by Weissman, 1989) from the Diagnostic Interview Schedule (DIS;

Robins et al., 1981) regarding thoughts about death and suicide. All subjects also completed the following questionnaires: the Beck Hopelessness Scale (BHS; Beck et al., 1974), the Self-rating Anxiety Scale (SAS; Zung, 1971), the Self-rating Depression Scale (SDS; Zung, 1965), and the Suicide Risk Scale (SRS; Plutchik et al., 1989). Student's t-test for unrelated samples and the chi-square test were used where appropriate.

RESULTS

As expected, the group of panic patients scored significantly higher on the SAS, SDS, and BHS ($p < 0.001$, Student's t-test) than the normal control group, with mean scores of 46.73 (SD 8.88), 45.25 (SD 8.13), and 7.04 (SD 4.43), respectively. Controls had mean scores of 25.90 (SD 3.31), 26.92 (SD 4.56) and 2.76 (SD 2.45), respectively. What we had not expected, however, was that the mean score on the SRS would also be higher for the patient group (4.36, SD 2.53) than for the control group (0.60, SD 0.99). An item analysis (Table 1) puts this finding into perspective. A certain subset of items (items 1 to 9) account for all of the differences between the two groups, and this will be discussed later.

As for the four DIS items, item 1 - "*Thought a lot about death*" - and item 2 - "*Felt like you wanted to die*"- were answered in a positive way significantly more often by the patient group than by the controls (chi-square test, $p = 0.002$ and $p = 0.004$, respectively). The responses to item 3 - "*Felt so low, thought about suicide*"- and item 4 - "*Made suicide attempts*"- were not significantly different.

Table 1. Item analysis of the Suicide Rating Scale, panic disorder patients compared to controls

<i>Item</i>	<i>Chi-square</i>	<i>p</i>
1 Do you take drugs such as aspirins or sleeping pills regularly?	14.91	< 0.001
2 Do you have trouble falling asleep?	24.00	< 0.001
3 Do you sometimes feel that you will lose control of yourself?	44.44	< 0.001
4 Do you have little interest in being with people?	20.48	< 0.001
5 Do you feel that your future will be more unpleasant than pleasant?	23.45	< 0.001
6 Do you ever feel that you are worthless?	32.19	< 0.001
7 Do you feel hopeless about your future?	10.69	0.001
8 Do you often feel so frustrated that you just want to lie down and quit struggling altogether?	12.36	< 0.001
9 Do you feel depressed now?	17.64	< 0.001
10 Are you separated, divorced or widowed?	0.10	0.75
11 Has anyone in your family ever tried to commit suicide?	1.00	0.31
12 Have you ever been so angry that you felt you might kill someone?	3.05	0.08
13 Have you ever thought about committing suicide?	5.00	0.25
14 Have you ever told anyone you would commit suicide?	1.89	0.17
15 Have you ever tried to commit suicide?	1.01	0.31

DISCUSSION

Our hypothesis was that *pure* PD patients (without axis I or II comorbidity) would not show an elevated risk for suicide. Relying on findings by Beck et al. (1991), Friedman et al. (1992), and Warshaw et al. (1995), we assumed that the higher suicidality found by Weissman et al. (1989) could be attributed entirely to lifetime comorbidity of depression, addiction, and personality disorders. Therefore, in the present study, we carefully excluded any and all PD subjects with comorbid pathology. In particular we took great care to detect any clinically established lifetime depression.

As expected, patients had higher scores on the BHS and SDS than the control group. PD is known to be a very disabling disease that significantly affects patients' quality of life. Higher scores on several items on the BHS and SDS may easily be attributed to the distress caused by the disease without its progressing to a formal depression. With regard to the higher patient score on the BHS, it is worth noting that Beck et al. (1990) showed a correlation between the BHS score and suicide risk. Yet, their cut-off score (a total of 9) was well beyond the mean of our patient group.

We found a higher total mean on the SRS for the patient group than for controls. A closer look by means of item analysis (Table 1), however, shows that patients differed from controls on the first nine items only. These items

address such psychological dimensions as feelings of frustration, worthlessness, depressed mood, and difficulty sleeping, all of which reflect the well-known reactive ‘demoralization’ in anxiety disorders (Breier et al., 1984). The other items (10 to 15) relate to the more specific sphere of suicidality, e.g., as suicidal ideation and past attempts, aggression, and demographic factors (marital status, past suicide of relatives). On none of these six items were there any differences between PD patients and normal controls. Thus, it is quite likely that the answers to the first nine items of the SRS reflect the impaired quality of life of the PD patient, as described by Markowitz et al. (1989) and others, rather than a genuine increased suicidality.

Similar arguments may be used to explain the answers to the four DIS items. The fact that item 1 - *“Thought a lot about death”* - was scored positively more often by the patients than controls is not surprising since one of the core elements of panic attacks is an overwhelming sense of fright and fear of dying from the attack. The aforementioned demoralization might also be the reason patients ruminate about death in general.

Item 2 - *“Felt like you wanted to die”* - was also answered positively more often by the patient group. At first, this difference seemed unexpected and was more difficult to explain in terms of our original hypothesis. Why should PD patients more often feel the (passive) wish to be dead than controls? One possible explanation, however, could again be demoralization. Although the wish to be dead may be interpreted as far more serious than common demoralization, it might reflect the unbearable feeling of total loss of control that occurs during panic attacks. This does not necessarily imply any intention to actively put an end to one’s life. Moreover, as items 3 and 4 - *“Felt so low, thought about committing suicide”* and *“Made suicide attempts”* - show that PD patients do not report more suicidal thoughts than controls. Nor did any subject in either group ever make an attempt to commit suicide.

CONCLUSIONS

Three conclusions can be drawn from our findings. First, PD patients are more preoccupied with death in general than are controls. Second, PD patients sometimes have a (passive) wish to be dead. Third, this rumination occurs without the actual intent of killing themselves. In line with other current research, we did not find a higher suicide risk for the PD patient group than for controls. The strength of this study lies in the fact that comorbid disorders were meticulously excluded, both those occurring at the time of the study and those occurring at some time in the past. We explicitly controlled for well-known factors that could contribute to suicide risk in psychiatric patients (addiction, borderline personality disorder, and affective disorder).

Yet, we must be cautious in drawing the conclusion that, in everyday life, PD patients are not at risk for suicide. Comorbidity cannot be ignored in anxiety disorders in general, and in PD in particular, in relation to suicide. Our sample may not be representative of PD patients presented in clinical practice because comorbid depressive disorder is concurrently present in approximately 30% of cases; this grows to 60% if one includes lifetime comorbidity as well (Breier et al., 1984, Griez and Overbeek, 1997). Personality disorder is diagnosed in almost 40% (Wetzler and Sanderson, 1995) and substance abuse in about 40% of cases (Wittchen and Essau, 1996), with some overlap. Nevertheless, these considerations do not affect our conclusion that a diagnosis of PD by itself (so called *pure* PD) is not associated with a higher risk for suicide.

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6. SLEEP COMPLAINTS IN PANIC DISORDER PATIENTS

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ABSTRACT

Background: Patients suffering from anxiety disorders often report difficulty sleeping.

Purpose: The present study assesses the prevalence of sleep complaints in panic disorder (PD) patients, compares them with sleep complaints in a normal population, and investigates the role of comorbid depression and nocturnal panic attacks in sleep complaints in the PD patients.

Method: Seventy PD patients and 70 healthy controls were asked about their subjective sleep characteristics by means of the Sleep-Wake Experience List, which assesses sleep/arousal complaints over a 24-hour period.

Results: Sixty-seven percent of the PD patients reported sleep complaints compared to 20% of the controls. Seventy-seven percent of the PD patients with comorbid depression and/or nocturnal panic attacks reported sleep complaints versus 53% of the 'pure' PD patients.

Conclusion: PD patients demonstrate a higher prevalence of sleep complaints than normal controls; this can only partly be explained by comorbid depression or by the presence of nocturnal panic attacks.

INTRODUCTION

Psychiatric disorders are frequently accompanied by sleep complaints (Benca et al., 1992). Most conspicuous are mood disorders, with insomnia being reported in about 80% of the afflicted cases (Szuba, 2001). Polysomnographic studies have further shown that a shortened REM latency is one of the most consistent deviations in the sleep of depressed patients (Reynolds and Kupfer, 1987).

Patients suffering from anxiety disorders also often report difficulty sleeping. For example, in generalized anxiety disorder (GAD) and in post-traumatic stress disorder (PTSD), sleep complaints are one of the major symptoms. Most polysomnographic studies in those disorders suggest some objective impairment (Mellman, 2003). In panic disorder (PD), sleep complaints do not belong to the diagnostic criteria, but in clinical practice they are often encountered as accompanying phenomena. Surveys have documented increased sleep complaints in PD patients compared to control populations, and some polysomnographic studies have found decreases in sleep efficiency and sleep duration in PD. In general, sleep impairment was strongly associated with comorbid depression (Mellman, 2003).

The relationship between sleep and PD is particularly interesting because impaired arousal regulation has been postulated as a potential underlying pathophysiological mechanism in PD (Lepola et al., 1994). Panic attacks may arise either from transient hyperarousal (e.g. anticipation anxiety, exercise), or from transient hypo-arousal (relaxation-induced panic) (Mellman, 2003). Others have put forward that PD is associated with chronic hyperarousal. During sleep this is reflected in more frequent nightly awakenings and more movements, except in nights with nocturnal panic attacks (Uhde et al., 1984; Brown and Uhde, 2003).

A potential link between PD and sleep complaints is the presence of nocturnal panic attacks. About 33% of PD patients report recurrent nocturnal panic attacks and some 69% report experiencing them at some point in their lives (Mellman and Uhde, 1989b). Nocturnal panic attacks not only induce sleep problems because of their sleep-interrupting nature, but also because of subsequent anticipatory anxiety, phobic anxiety of going to sleep, sleep avoidance and, finally, sleep deprivation, which may further aggravate anxiety. With respect to the phenomenology of nocturnal panic attacks, one study showed that these attacks do not differ from daytime attacks in mean severity, duration, or number of symptoms per attack (Krystal et al., 1991).

Another common factor of PD and sleep complaints may be the presence of a comorbid mood disorder. Comorbidity of PD and depression is high, with a reported point-prevalence of about 30-40 % (Lesser et al., 1989; Lepine, 2001).

The strong association between depression with sleep complaints on one hand, and the association between depression and PD on the other, suggests that depression may mediate the relation between PD and sleep complaints.

A common shortcoming in the assessment of sleep complaints is the lack of a systematic assessment (van Diest et al., 1993). The duration of the sleep complaints is not always reported; consequently, a distinction cannot be made between transient (i.e., < 3 weeks) and chronic (i.e., > 3 weeks) sleep complaints. Furthermore, most studies do not consider the entire 24-hour period. Within a 24-hour period, sleep complaints are distinguished as problems initiating sleep, maintaining sleep, early morning awakening, difficulty waking up, tiredness upon waking up, and daytime sleepiness.

In the present study, we tested the hypothesis that PD is associated with an increased prevalence rate of subjective sleep complaints. In addition, we tested the hypothesis that the increased prevalence of sleep complaints in PD is accounted for by comorbid depression and/or nocturnal panic attacks in these patients. For practical reasons we combined PD patients with nocturnal panic attacks and with comorbid depression into one group, the ‘comorbid’ group. The authors chose to use the term ‘comorbid’ for these cases –despite the fact that the term does not fully apply here since nocturnal panic attacks are a symptom of the disorder PD. We therefore put the description in quotation marks. We expected an increased prevalence of sleep complaints in PD patients with comorbid depression and/or nocturnal panic attacks compared to PD patients without these characteristics (the ‘pure’ group). We also expected that the prevalence of sleep complaints in PD patients without comorbid depression and nocturnal panic attacks would be similar to that of healthy controls.

METHODS

Participants: Participants were 70 patients recruited at the Academic Anxiety Center, Maastricht, the Netherlands, an outpatient clinic that specializes in the diagnosis and treatment of anxiety disorders. All patients had a psychiatric interview conducted by a MD and they were screened by means of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Psychiatric diagnoses were made according to DSM-IV criteria (APA, 1994) and were confirmed in consensus with two qualified psychiatrists. Patients with a primary DSM-IV axis I diagnosis of PD (with or without agoraphobia) were asked to participate. Patients with other axis I disorders were excluded, except for current depressive disorder or dysthymia. Care was taken to obtain a history of all medication taken in the past 3 months. Patients who used benzodiazepines on a regular basis were excluded. Also, patients on older antidepressants (e.g., tricyclics) that are known to have rather sedative side

effects were excluded. The use of SSRIs was accepted as they are the first-choice pharmacological treatment for PD. However, because SSRIs can affect sleep (Masand and Gupta, 1999), we performed a post-hoc analysis to test whether the use of SSRIs influenced the presence of sleep complaints in our sample. Forty-four PD patients were female (63%) and 26 (37%) were male. Their combined mean age was 36.9 ± 10.9 years.

Healthy controls were recruited by advertisements. They were age- and gender- matched with the patient group. The mean age of the 44 female and 26 male controls was 35.8 ± 11.1 years. None of them used psychotropic medication. They too were screened with the MINI.

All participants gave informed consent.

The Sleep-Wake Experience List: Sleep complaints were assessed by means of the Sleep-Wake Experience List (SWEL) (van Diest et al., 1993). This instrument consists of 15 items covering six types of sleep complaints as they occur within a 24-hour period. These complaints include problems initiating sleep, maintaining sleep, early morning awakening, difficulty waking up, tiredness upon waking up, and daytime sleepiness. The separate sleep complaints were coded 'chronic' if the complaint was described both as 'rather severe' to 'very severe' and as 'often present' or 'always present' for a period of 3 months. Thus, the severity and frequency of occurrence were combined to code as sufficiently severe to make a chronic sleep complaint. Other details of the SWEL have been described elsewhere (van Diest, 1990; van Diest et al., 1993). For this study, the SWEL was extended with additional items to assess the occurrence of nocturnal panic attacks. Participants were instructed to base their answers upon the last 3 months.

Statistical analysis: The chi-square test (SPSS for Windows) was used to examine associations of PD with sleep complaints. Students' T-test was applied to compare baseline characteristics of the 'pure' versus the 'comorbid' group. Significance levels were based on two-tailed tests with a p -value ≤ 0.05 .

RESULTS

Of the 70 PD patients, 21 (30%) suffered from a comorbid depression ($N=16$) or dysthymia ($N=5$). The severity of depression in this group was mild, a mean score of 18.7 (SD 6.8) on the Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979) and a mean score of 54.1 (SD 7.4) on the Selfrating Depression Scale (Zung, 1965).

Some 31 patients (44%) reported nocturnal panic attacks in the last three months. The frequency of the nocturnal panic attacks was as follows: 1-2 in 13 patients; 3-4 in 8 patients; 5-6 in 6, and more than 6 in 4 patients. Twelve PD patients (17%) had both depression and nocturnal panic attacks.

Combining these conditions yielded 40 patients with either one or both of these characteristics, the 'comorbid' group. The 30 PD patients without any of these characteristics made up the 'pure' group. Nocturnal panic attacks were not associated with comorbid depression ($\chi^2 = 2.01$; $df = 1$; $p = 0.12$). The subgroups did not differ on severity measures for PD. The mean Panic and Agoraphobia Scale (PAS, Bandelow, 1995) for the 'comorbid' group was 29.4 (SD 8.3), versus 27.1 (SD 8.1) for the 'pure' group. Mean scores on the Fear Questionnaire (FQ, Marks and Mathews, 1979) was 52.1 (SD 26.1) for the 'comorbid' group versus 40.9 (SD 24.9) for the 'pure' group. The use of SSRIs was similar in the 'comorbid' and the 'pure' groups ($\chi^2 = 0.18$; $df = 1$; $p = 0.67$). Post-hoc analysis showed no difference in prevalence of sleep complaints between PD patients who used SSRIs and those who did not ($\chi^2 = 0.66$; $df = 1$; $p = 0.29$).

Prevalence of sleep complaints

PD patients (N=70) versus healthy controls (N=70): Chronic sleep complaints during the past 3 months were reported by 67% of patients and by 20% of controls. The significant association between PD and sleep complaints ($p < 0.01$) supported our first hypothesis; therefore, we tested whether this increased prevalence of sleep complaints in PD patients was due to comorbid depression and/or nocturnal panic attacks in those patients.

'Pure' (N=30) versus 'comorbid' PD patients (N=40): The prevalence of sleep complaints was significantly higher in the 'comorbid' group (77%) than that in the 'pure' group (53%; $p = 0.03$), which supported our second hypothesis.

'Pure' PD patients (N=30) versus Controls (N=70): The prevalence of sleep complaints in the 'pure' PD group (53%) was significantly higher than that in the control group (20%; $p < 0.01$), which did not support our second hypothesis. A post-hoc analysis to assess the role of the SSRIs in this comparison yielded the same results: PD patients without depression, nocturnal panic, or medication also reported significantly more sleep complaints than did healthy control subjects.

Nature of sleep complaints

In view of these results we decided to investigate the specific sleep complaints reported by the different subgroups of patients and we compared them to the sleep complaints reported by healthy controls (Table 1).

PD patients versus Controls: PD patients reported complaints initiating sleep, maintaining sleep, early morning awakening, difficulty waking up, tiredness upon waking up and daytime sleepiness significantly more often ($p < 1$ in Table 1).

'Pure' versus 'comorbid' PD patients: PD patients with comorbid depression and/or nocturnal panic reported having problems maintaining sleep significantly more

often than 'pure' PD patients (p_2 in Table 1). The two groups did not differ significantly in any of the other sleep complaints.

Pure' PD patients versus Controls: 'Pure' PD patients reported having problems initiating sleep, tiredness upon waking up, and daytime sleepiness significantly more often than controls (p_3 in Table 1).

Table 1. Nature of sleep complaints in PD patients, patient subgroups, and controls (%)

<i>Sleep measure</i>	<i>All PD (N=70)</i>	<i>'comorbid' PD (N=40)</i>	<i>'pure' PD (N=30)</i>	<i>Controls (N=70)</i>	p_1^a	p_2^b	p_3^c
Initiating sleep	24.2	32.5	13.3	1.4	<0.01	0.06	0.03
Maintaining sleep	24.2	35.0	10.0	1.4	<0.01	0.01	0.08
Early morning awakening	7.1	10.0	3.3	0.0	0.03	0.28	0.30
Difficulty waking up	27.1	27.5	26.6	12.8	0.03	0.58	0.08
Tiredness upon waking up	38.6	40.0	36.6	8.6	<0.01	0.49	0.01
Daytime sleepiness	41.4	50.0	30.0	4.2	<0.01	0.08	0.01

a: p_1 = PD compared with Controls

b: p_2 = 'Pure' PD compared with 'comorbid' PD

c: p_3 = 'Pure' PD compared with Controls

DISCUSSION

This study demonstrates that PD patients suffer from sleep complaints more frequently than controls. PD patients with comorbid depression and/or nocturnal panic attacks report sleep complaints more frequently than 'pure' PD patients. Moreover, 'pure' PD patients have a higher prevalence of sleep complaints than healthy controls. Apparently, comorbid depression and/or nocturnal panic contribute to sleep complaints in PD patients, but they are not sufficient to explain the higher prevalence of sleep complaints in PD.

To date, there have been no recent studies on subjective sleep quality in PD patients. Few studies exist that focus on sleep disturbances in this disorder. Sheehan et al. (1980) found that in a sample of 57 PD patients (not excluding comorbid depression and nocturnal panic), approximately 70% reported disturbed sleep. Mellman and Uhde (1989b) conducted a self-report sleep survey in 45 PD patients compared with 26 healthy controls. A majority of these patients (58%) also had lifetime depressive disorder; none had a current

depression. One-third reported recurrent nocturnal panic attacks. Two-thirds of PD patients reported general insomnia, as did 35% of controls. They found no differences regarding early insomnia, but patients reported significantly more middle and late insomnia than healthy controls. Our finding that PD patients have more difficulty initiating sleep than controls is not in line with earlier reports (Mellman and Uhde, 1989b). However, because of different operational criteria, we should be cautious when comparing the results of these two studies.

Our second hypothesis, regarding the association of sleep problems in PD with comorbid depression and /or the presence of nocturnal panic attacks, was partly supported by the finding that 'comorbid' PD patients reported suffering from sleep complaints more frequently than 'pure' PD patients did. The difference between the 'pure' and 'comorbid' group was specifically reflected in the category of maintaining sleep, where significantly more 'comorbid' PD patients reported having problems than their 'pure' counterparts did. This finding could be explained by the nature of nocturnal panic attacks as well as by the comorbid depressive disorder. Panic attacks that spontaneously occur during a patient's sleep will certainly disrupt sleep and keep the patient from getting a good night's rest. Moreover, as difficulty maintaining sleep is a symptom in depressive disorder, it is not surprising that PD patients with a comorbid depression have problems within this specific symptom category in particular.

Comparing the 'pure' PD patients with the healthy control group yielded unexpected results. The prevalence rate of sleep complaints appeared to be higher in the 'pure' PD patients, and in several individual categories of sleep complaints the PD patients without depression and without nocturnal panic attacks had significantly more complaints than did healthy controls. Our results showed significantly more difficulties for the 'pure' PD patient group in the categories of initiating sleep, waking up tired, and daytime sleepiness. Therefore, 'pure' PD patients also seem to suffer from a poor quality of sleep, regardless of comorbid depression and night panic attacks. Combining this finding with the previously discussed difference between PD patients with and without depression and nocturnal panic, we infer that PD alone can lead to problems initiating sleep, waking up tired and daytime sleepiness. The additional presence of a comorbid depression or of nocturnal panic gives rise to further problems maintaining sleep.

In patients with depressive disorder, the presence of subjective sleep complaints has been shown to correlate with objective sleep parameters. In fact, correlations between subjective and objective sleep measures were found to be quite good in a group of depressed patients and controls (Armitage et al., 1997). It might be interesting to link our findings on subjective sleep

characteristics to those from studies that focus on objective sleep parameters in PD patients. Studies on sleep EEG studies in PD are, however, far from unequivocal. Differences in methodology, comorbidity status, and definitional issues apply here. Most authors have reported only limited changes in sleep duration and sleep architecture in PD (Arriaga et al., 1996; Ferini-Strambi et al., 1996; Landry et al., 2002; Stein et al., 1993b). Stein et al. (1993a) already noted the apparent dissonance between PD patients' subjective sleep complaints and the paucity of polysomnographic abnormalities detected in most physiological studies. Some positive studies, for example, include an early study by Mellman and Uhde (1989a) and one by Sloan et al. (1999). However, though most earlier studies on sleep EEG fail to show clear differences between PD patients (without depression) and controls, one recent study suggests that there are some overall differences (Saletu-Zyhlarz et al., 2000). In this study, both objective, and subjective parameters were measured. Eleven PD patients were compared with 11 healthy controls. In baseline objective measurements they report a significant decrease in sleep efficiency, total sleep time, and increased middle and late insomnia in the absence of REM differences. In addition, subjective sleep quality was worse for the patient group. This could indicate that advanced technological methodology may allow more subtle objective differences to reflect subjective clinical differences. If sleep disturbances in PD are insufficiently accounted for by comorbidity of depression or nocturnal panic, there must be some feature related to the PD itself that also gives rise to problems with quality of sleep. Arousal dysregulation is an obvious possibility, as it is hypothesized to be an underlying mechanism in PD (Lepola et al, 1994). Besides the state of arousal during the panic attack itself, arousal dysregulation during the 24-hour period could also give rise to complaints of diminished sleep quality and daytime sleepiness. Arousal also relates to the functioning of the autonomic nervous system, which is known to be more unstable in PD patients than in controls. Faravelli et al. (1997) showed a decrease in mean flow velocity of the right middle cerebral artery in response to the tilting table test in PD patients, suggesting autonomic dysfunction. Several investigators have reported a decreased heart rate variability in PD patients (Klein et al., 1995; Sloan et al., 1999), and PD patients seem to have a more unstable respiratory pattern than normal controls (Wilhelm et al., 2001). The precise interrelations between arousal, sleep and autonomic instability in PD patients remain unclear. Further studies, including objective sleep registration studies, together with monitoring physiological parameters, in pure PD patients without nocturnal panic attacks, would be needed to clarify this issue. Other, potentially related factors should also be considered. For instance, PD has been associated with a higher selective attention to physical sensations suggestive of anxiety (anxiety sensitivity), leading to 'catastrophic interpretation' of these bodily sensations (Clark, 1986).

Another factor that might influence sleep in PD is the extreme fatigue that may occur after a panic attack. This fatigue was found to be the most prominent post-attack phenomenon in 72% of PD patients (Starcevic, 1991). Finally, a number of limitations of this study need to be mentioned. The sample size, particularly of the 'pure' PD group, should have been larger. Though many factors can influence sleep (e.g. medical conditions as pain or dyspnea or social circumstances, Drake et al., 2003), we did not address any other confounders. Also, as mentioned briefly before, it would have been of great value if we had included objective sleep parameters. Nevertheless, despite these limitations, this study indicates an association between PD and subjective sleep complaints, irrespective of comorbid depression or nocturnal panic.

CONCLUSIONS

From these data we conclude that PD patients suffer from sleep complaints more frequently than normal controls. The higher prevalence of sleep complaints in PD patients can only partly be explained by comorbid depression or by the presence of nocturnal panic attacks.

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**7. BLOOD-INJURY RELATED PHOBIC AVOIDANCE AS
PREDICTOR OF NONRESPONSE TO
PHARMACOTHERAPY IN PANIC DISORDER WITH
AGORAPHOBIA**

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ABSTRACT

Background: Several factors have been investigated as possible predictors of nonresponse to pharmacotherapy in Panic Disorder (PD) patients. In 1995 a study was published by Slaap et al. in the *Journal of Affective Disorders* that found high Blood-Injury phobia scores on the Marks and Matthews Fear Questionnaire were predictive for a worse treatment-outcome for drug treatment in PD.

Methods: The present paper describes a replication study with 61 PD patients, by means of a retrospective chart analysis, who were assessed at baseline and after 12 weeks of SSRI-treatment. Nonresponse was defined as still having panic attacks. Response was defined as absence of panic attacks and/or a reduction of at least 50% on the FQ Agoraphobia subscale.

Results: Twenty (32%) patients were nonresponders. Nonresponders had a higher score on the FQ Blood-Injury subscale more often (55%) than responders (19.5%), significant at $p=.008$. These results fully support the findings of Slaap et al. Implications of these findings are further discussed.

Limitations: Limitations of this study are the retrospective design, and the absence of other psycho-physiological parameters of the specific blood-injury phobic complex.

Conclusions: However, it is tentatively concluded that the presence of comorbid blood-injury related phobic symptoms negatively affects treatment for panic disorder and agoraphobia.

INTRODUCTION

Panic Disorder (PD) is a common psychiatric illness that causes considerable short- and long-term morbidity. In the absence of effective therapy, PD tends to become a chronic disorder with a low tendency of spontaneous remission (Faravelli et al., 1995; Katschnig and Amering, 1998).

Pharmacological treatment, either with a specific serotonin reuptake inhibitor (SSRI), or one of the older tricyclic antidepressants (TCAs), or even a monoamine oxidase inhibitor (MAOI) has proven effective in the majority of patients (Feighner, 1999). Also cognitive behavioral therapy (CBT) is an effective treatment for PD. Although a recent study by Fava et al. (2001) showed that, in spite of successful symptom reduction by CBT, residual symptoms and impaired psychological well-being must not be underestimated. However, a proportion of PD patients does not respond to any of the currently available treatments. Many factors have been investigated as being possible predictive of nonresponse to both short-term and long-term treatment in PD (for a review, see Slaap and den Boer, 2001). The potential predictors in pharmacotherapy that have been most often investigated are associated with demographic variables, illness variables, or comorbidity. While demographic variables failed to give clear-cut indications of nonresponse, some illness-related variables as a long history of PD, frequent panic attacks, and severe agoraphobic avoidance appeared to be negatively correlated with the response to treatment. Some studies found the presence of a comorbid depression to predict nonresponse, mainly on the long term. Personality disorders, or even personality disorder characteristics, in some studies are found to predict nonresponse, whereas other studies find no relationship between personality and treatment outcome but on the contrary even found a significant change in personality disorder characteristics with effective PD treatment (Hofmann, 1998). One may tentatively conclude that long duration of illness and severe agoraphobic avoidance are the most robust predictors of nonresponse to drug treatment, particularly in the long term.

Some years ago, Slaap et al. (1995) reported on an unexpected psychometric dimension they found to be predictive of treatment outcome for PD. They conducted a study to determine clinical baseline variables of 44 PD patients, screening which one might identify responders and nonresponders. It was found that one of the best predictors of nonresponse to drug treatment, in this particular case 29 subjects on brofaromine (a MAOI) and 15 on fluvoxamine (a SSRI), was a high baseline score on the blood-injury phobia subscale of the Fear Questionnaire (Marks and Mathews, 1979). This intriguing finding, and its possible theoretical implications, has received little attention in the literature, which led us to undertake this replication study in our own patient population.

We hypothesized that the scores on the subscales of the Fear Questionnaire were irrelevant for treatment outcome in PD patients. Responders and nonresponders were expected to show the same mean scores on these subscales, and an equal percentage of 'high' against 'low' scorers.

METHODS

Sample

Patients were referred for treatment to the Academic Anxiety Center Maastricht, the Netherlands, a tertiary outpatient clinic, specializing in anxiety disorders. According to standard procedures in our clinic, all patients were evaluated by means of a psychiatric interview, with special emphasis on anxiety and affective spectrum symptoms. A diagnosis was made according to DSM-IV (APA, 1994) criteria (or DSM-III-R; APA, 1987; whichever current at the time of referral), and confirmed by two experienced psychiatrists.

Included for this retrospective chart analysis were 61 PD patients, all of them had agoraphobia. Exclusion criteria were other axis I disorders (including depressive disorder) as a comorbid diagnosis, and missing data at baseline or after twelve weeks of medication.

Treatment

After completion of the diagnostic procedure, patients were offered a combined psychopharmacological and behavioral treatment. Initially, in the first phase, patients received pharmacotherapy, i.e., a prescription for one of the current SSRIs, and were regularly seen for a global clinical evaluation. Fifteen patients were on paroxetine (dosage from 20 to 50 mg) and 46 patients were on fluvoxamine (dosage from 150 to 250 mg). There were no differences between both groups at baseline and after drug treatment. The second psychometric assessment took place between week 10 and 12, before the planned start of behavior therapy, based on exposure and response-prevention intervention. The present study therefore only covers the first phase of treatment.

Assessment

Patients were evaluated by means of a battery of standardized questionnaires and structured interviews, among which were the Fear Questionnaire FQ (Marks and Mathews, 1979) and the Montgomery-Asberg Depression Rating Scale MADRS (Montgomery and Asberg, 1979). The FQ is a self-rating scale, consisting of three subscales, of five items each, to be scored from 0 to 8, regarding Agoraphobia, Social Phobia, and Blood-Injury Phobia. Maximum score for each subscale is 40, total maximum thus 120. The MADRS is an investigator rated scale, consisting of 10 items on depressive symptoms, to be

scored from 0 to 6. Patients also standard received a physical examination, including blood tests. Panic attack frequency and intensity was registered, regarding 2 weeks prior to the start of medication and after ten to twelve weeks of pharmacotherapy.

Response in our study was defined as a total absence of panic attacks in week 10-12 until the end of behavior therapy, or a reduction of at least 50% on the initial score on the Agoraphobia subscale of the Fear Questionnaire. This definition on the whole is similar to the definition used in the original study conducted by Slaap et al. (1995). The only difference with the Slaap et al. study is the period in which we measured the presence or recurrence of panic attacks: we included panic attacks that occurred during the phase of combined drug and behavior therapy. If patients were free of attacks in week 10 to 12, but attacks recurred somewhere during behavior therapy, they were considered nonresponders. Otherwise, if still having panic attacks during week 10 to 12, but afterwards, during behavioral treatment becoming panic free, patients were also considered as nonresponders. This makes our definition of response and nonresponse stricter than the original study's definition because we include a longer-term response.

Statistical Analysis

Statistical analysis was conducted with SPSS-PC, version 7.5. Differences between responders and nonresponders were analyzed by ANOVA on baseline variables MADRS, FQ total score (FQT), FQ Agoraphobia (FQA) subscore, FQ Blood Injury (FQB) subscore, and the FQ Social Phobia (FQS) subscore. Categorization of high versus low scorers on the FQ subscales was defined at a cut-off score of 20 on each subscale. These data were tested with Fisher's exact test (two-tailed). These scores were used as indicator variables to investigate the influence of phobic symptoms on nonresponse. A logistic regression analysis was carried out for all significant baseline variables, with backwards elimination, to make a best-fitting model. These procedures were identical to the procedures used in the Slaap et al. study.

RESULTS

Patient demographics and clinical variables at baseline are shown in Table 1. The mean age of the 61 patients was 37.7 (SD 9.3) years. Thirty-seven (61%) were female, with a mean age of 35.7 (SD 9.4) years. The mean age of the 24 male subjects was 39.2 (SD 9.0) years (NS).

Table 1. Mean scores for Responders and Nonresponders at baseline

	<i>Responders (N=41)</i>	<i>Nonresponders (N=20)</i>	<i>p</i>
Mean age	37.7 (± 9.3)	37.4 (± 8.8)	NS
Male:female ratio	15:26	9:11	NS
<i>MADRS</i>	6.3 (± 4.2)	7.1 (± 4.0)	NS
<i>FQ Total</i>	50.1 (± 21.1)	65.7 (± 22.7)	0.014
<i>FQ Agoraphobia</i>	23.4 (± 10.6)	28.8 (± 9.4)	NS
<i>FQ Blood Injury</i>	11.5 (± 8.2)	18.4 (± 12.7)	0.011
<i>FQ Social Phobia</i>	15.2 (± 9.5)	18.5 (± 7.5)	NS

Forty-one patients were found to be responders by our definition, whereas 20 patients did not meet the criteria for response. Gender distribution in the responder group was 26 female and 15 male, in the group of nonresponders 11 were female and 9 male (NS). Mean age for responders (37.7, SD 9.3) and nonresponders (37.4, SD 8.8) did not differ.

Mean FQ scores at baseline for both groups are shown in Figure 1. The mean MADRS for responders (6.3; SD 4.2) and nonresponders (7.1; SD 4.0) did not differ significantly at baseline. The mean baseline FQA neither showed any significant difference, responders scored 23.4 (SD 10.6) and the nonresponders 28.8 (SD 9.4). Also the FQS (before treatment) did not differ significantly between responders (15.2; SD 9.5) and nonresponders (18.5; SD 7.5). The means on the FQB (and the FQT), however, did differ. The mean baseline score for responders on the Blood Injury Phobia subscale was 11.5 (SD 8.2) and for nonresponders 18.4 (SD 12.7), significant at $p=.011$. Also the baseline FQT scores were significantly higher (at $p=.014$) for the group of nonresponders (65.7; SD 22.7) than for the responders (50.1; SD 21.1), largely attributable to the FQB score, because if taken together, the subscores on FQA and FQS did not differ significantly between responders and nonresponders.

Figure 1. Mean scores of responders vs nonresponders on the Fear Questionnaire and its subscales at baseline

Looking for possible predictors, we used indicator variables, derived from dichotomizing scores on the FQ-subscales in ‘high’ (≥ 20) and ‘low’ (< 20) scorers. Combinations of subscales are ‘high’ scorers if on all individual subscales the subscores are above the cut-off of 20. The indicator variables for the FQ-subscales and the combinations of subscales are given in Table 2.

Table 2. Indicator variables of FQ-subscales and their combinations.

	Responders (N=41)		Nonresponders (N=20)		p
	%	N	%	N	
High FQA	61	25	80	16	NS
High FQB	19.5	8	55	11	0.008
High FQS	36.6	15	45	9	NS
High FQA + FQB	19.5	8	50	10	0.019
High FQA + FQS	24.4	10	45	9	NS
High FQB + FQS	2.4	1	40	8	<0.001
High FQA + FQB + FQS	2.4	1	40	8	<0.001

For the individual subscales, only the Blood-Injury score at baseline significantly differs in percentage between the responders (19.5% scoring as high) and nonresponders (55% ‘high’), Fisher’s exact test $p=.008$. Combinations of subscores turn out to show significant differences in percentage of high versus low scoring patients, only if the FQB is included. For FQA together with FQB 19.5% responders against 50% of nonresponders

score 'high' ($p=.019$); FQB and FQS together show a 2.4% 'high' responders against 40% 'high' nonresponders ($p<.001$); if combining all three subscales FQA and FQB and FQS 2.4% of responders and 40% of nonresponders are 'high' scorers ($p<.001$)

For the prediction of nonresponse to drug therapy a regression analysis on all significant baseline variables (high FQB, high FQB + high FQA, high FQB + high FQS, high FQB + high FQA + high FQS) was carried out. Every single baseline variable significantly predicted nonresponse ($p<.05$). A best-fitting model was also calculated by carrying out a logistic regression analysis with all significant variables in the initial solution. The backwards elimination process resulted in a prediction based on one variable (set of variables) only. The variable 'having a high score on the FQA and FQB and FQS' was the only variable left in the equation. With this equation, the overall percentage correctly classified patients was 80.3%. Forty responders (97.6%) and 9 nonresponders (45%) were correctly classified. Incorrectly classified was 1 responder as nonresponder, and 11 nonresponders (55%) as responders. The fit of the model was reasonable (Chi-square 3.33; $p=.012$). Prediction based on only the variable high-low FQB would provide a correct overall percentage of 72.1%, with 55% of nonresponders and 80.5% of responders correctly classified (Chi-square 7.67; $p=.006$).

DISCUSSION

The present results show that scores on the Blood-Injury phobia subscale of the Fear Questionnaire are predictive for PD treatment outcome. Higher baseline scores on the FQB were found in the group of patients that did not respond well to drug therapy. The findings of Slaap et al. (1995), based on a sample of 44 PD patients, were replicated in a larger sample of 61 patients.

Previous studies regarding the comorbidity among the anxiety disorders, have reported large prevalences of other anxiety disorders in PD (Di Nardo and Barlow, 1990). Reported comorbidity rates of simple phobia in PD vary between 6.3% and 46.6%, and a comorbid social phobia occurs in 9.6% to 40.7% in PD patients (Slaap et al., 1995). Subthreshold phobic symptoms, that do not reach full diagnostic criteria, are also very common in PD patients (Argyle et al., 1991). The presence of co-existing phobic symptoms reminiscent of simple phobia, seems to be a plausible explanation for the finding of relatively high FQ blood-injury phobia scores in PD patients. What is surprising, however, is the importance of these phobic symptoms for treatment outcome. Therefore the question arises whether there is a special relation between PD and blood-injury phobic symptoms. There are some data that provide some clues.

The special status of blood-injury phobia among the other specific phobias has been described (Marks, 1987, 1988; Öst et al., 1984). Blood-injury phobia differs from the other specific phobias, in that it has a stronger familial component, and because of its physiological characteristics: a unique biphasic response. In general, phobic stimuli elicit a rise in heart rate and blood pressure. In contrast, in blood-injury phobia, an initial short rise in heart frequency is very shortly afterwards followed by a robust bradycardia and hypotensive reaction. In 80% of cases this leads to a syncope or presyncope (Marks, 1987; Öst et al., 1984). Further, patients with blood-injury phobia show an abnormal hemodynamic response during experimental head-up tilt and are strikingly prone to vasovagal reactions, compared with normal controls (Accurso et al., 2001). Even in the absence of a blood or injury stimulus, blood pressure and heart rate decreased during the test. The authors state that fainting related to blood or injury may not be primarily due to a psychiatric condition, but rather due to dysfunction in the autonomic nervous system, which may secondarily lead to the phobia because of repeated syncopal events (Accurso et al., 2001). These studies show that blood-injury phobia is characterized by a special autonomic nervous system response. It is therefore conceivable that blood-phobic symptoms are also associated with autonomous dysregulation.

Previous studies have also related PD to a dysfunctional autonomic nervous system. Initial studies reported general autonomic dysfunctions in e.g. heart rate variability and blood pressure. However, more recent studies found no changes in systemic parameters (Faravelli et al., 1997; Wilhelm et al., 2001). Faravelli et al. (1997) have shown abnormalities in central parameters of sympathetic reactivity especially in the regulation of cerebral blood flow. By means of experimental tilting-table test, they found that PD patients responded to the manipulation with a lower mean flow velocity in the right middle cerebral artery, as compared with normal subjects.

From a different approach, an indirect argument in this direction could be the observation that patients with refractory neurocardiogenic (vasovagal) syncope can be effectively treated with a selective serotonin reuptake inhibitor paroxetine. Downregulation of postsynaptic serotonin receptors in the brain stem, resulting in a blunted response to rapid shifts in central serotonin levels, has been proposed as a possible explanation for this phenomenon (Di Girolamo et al., 1999).

The line of evidence towards a role of a disturbed autonomic nervous system in both blood injury phobia and PD is set, some (physiological) dysfunction here could explain a relationship between the two. The results of the present clinical study could support this link.

As well as a common physiological basis, another explanation for the present findings could lie in a link between PD and hypochondriasis. Hypochondriasis seems to be related to the anxiety disorders and shows some comparable

phenomenology. Its DSM classification with the somatoform disorders has been discussed but is now widely accepted (Noyes 1999). However, differentiation from specific illness phobia on the one hand, and PD on the other, is not always obvious. As often described before, PD patients frequently experience hypochondriacal concerns (Noyes et al., 1986; Starcevic et al., 1992; Furer et al., 1997). The high scores on the FQB we found in our PD sample could reflect ‘normal’ hypochondriacal preoccupations, as the items of the FQB relate to fear of injections or minor surgery, hospitals, sight of blood, thought of injury or illness, and going to the dentist. Some researchers found that the hypochondriacal symptoms of PD patients improve with treatment of the PD (and agoraphobia), and thus concluded that hypochondriasis was a prominent but secondary feature of the PD (Noyes et al., 1986; Fava et al., 1988c). Fava et al. (1988b) also showed that the common blood-injury phobic symptoms in PD patients, improve with nonspecific treatment (Fava, 1988c). They have used the same assessment tool of the FQ and its subscales as we did. Fava et al. (1988b) suggest that the presence of anxiety may be conducive to hypochondriacal concerns, including fear of blood and injury, and that such fears tend to remit when anxiety decreases. On the other hand, others describe hypochondriasis being present before the onset of the PD in about 50% of the comorbid patients (Furer et al., 1997; Fava et al., 1988a). This would point in the direction of true (symptom or syndrome) comorbidity and could complicate treatment, for hypochondriasis is known to be a condition that is rather resistant to therapy. Moreover, as PD patients, as well as hypochondriac patients, are very attentive to bodily symptoms and prone towards catastrophic misinterpretation, they could suffer more from normal SSRI side-effects, which could endanger their therapeutic compliance. Extensively reviewing cognitive aspects is beyond the scope of this paper, but for future research it would be interesting to include both cognitive and physiological assessments in PD treatment outcome. Bakker et al. (2002a, 2002b) recently have shown the relevance of belief in catastrophic misinterpretations during panic attacks for treatment outcome, and the differential effects of treatment modalities on the locus of control orientation in PD patients, CBT strengthening more internal locus of control, whereas medication influenced the external locus of control. This approach also seems highly relevant in studying blood-injury and hypochondriacal fears.

In sum, there seem to be at least two hypothetical lines of explanation regarding the role of subthreshold blood phobic symptoms in the treatment of PD with agoraphobia. Be it the comorbid blood-injury phobia with a common underlying physiological dysfunctional autonomic nervous system, or comorbid hypochondriac symptoms that are reflected in the score of the Fear Questionnaire Blood-injury subscale, the observed clinical importance seems to warrant further, more specific symptomatic and physiological investigation.

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*Section III. The affective spectrum in panic:
an experimental approach*

8. EXPERIMENTAL AFFECTIVE SYMPTOMS IN PANIC DISORDER PATIENTS

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ABSTRACT

Objective: To date CO₂ challenge tests in panic disorder (PD) patients focused on anxiety as the sole outcome measure. The aim of the present study was to assess a broader range of affective symptoms after a CO₂ challenge in a sample of PD patients with and without major depressive disorder (MDD).

Method: We administered a gas mixture of 35% CO₂ and 65% O₂ to 25 PD patients. Nine of these had a comorbid (current or lifetime) MDD and 16 patients did not meet criteria for MDD. At baseline, and immediately after the challenge, subjects were assessed on a list of panic symptoms (PSL), an adapted profile of mood states (POMS) regarding aggressive and depressive feelings, and visual analogue scales on anxiety (VAS-A), aggression (VAS-Ag) and depression (VAS-D).

Results: All patients reported an increase in anxiety symptoms. PD patients with comorbid lifetime depression showed a higher increase on both aggression and depression than did nondepressed PD patients.

Conclusion: These findings suggest that a comorbid mood disorder in PD patients is related to a response pattern to a CO₂ challenge with both anxiety and other affective symptoms. A panic challenge may be both depressogenic and aggressogenic, dependent on the comorbid disorder present.

INTRODUCTION

Controlled panic induction by means of experimental laboratory challenges is a well-known procedure. Hypersensitivity to the challenge is often accepted as indicative of panic disorder (PD). One of the available provocation methods is the inhalation of a gas mixture of 35% CO₂ with 65% O₂, originally described by Griez et al. (1987).

In PD patients, this intervention yields symptoms of anxiety as well as somatic symptoms that very much resemble a real-life panic attack. The method has been frequently used to investigate the underlying pathophysiological mechanisms of PD in laboratory setting (Griez and Schruers, 1998; Gorman et al., 1990; Perna et al., 1995). It is implicitly assumed that CO₂ only provokes anxiety. To date, other affective symptoms have not been assessed in a systematic way. However, it is generally known that anxiety disorders and mood disorders show large overlap of symptoms (Di Nardo and Barlow, 1990). Symptoms of depression, anxiety and aggression have been hypothesized to form a cluster, related to serotonergic (dys) functions (Apter et al., 1990; van Praag, 1998). According to this hypothesis, these serotonergic dysfunctions persist in times of remission. Moreover, feelings of aggression frequently are described in PD patients, and anger attacks have been proposed as a specific variant of panic attacks (Fava et al., 1990; George et al., 1989).

From syndromal perspective anxiety and mood disorders frequently coexist, e.g. approximately 30% of PD patients suffer from concurrent depression, and 60% of PD patients have a lifetime diagnosis of depression (Kaufman and Charney, 2000; Levine et al., 2001). Some authors have hypothesized that mood and anxiety disorders are two expressions of the one underlying affective spectrum disorder.

Therefore, it is interesting to assess if the supposedly panic-specific challenge test by means of CO₂ administration raises other affective symptoms, like aggression and depressive symptoms.

In the present study we assessed the presence of different affective symptoms in a CO₂ challenge paradigm. Along with anxiety, symptoms of the depressive and aggressive cluster were assessed. In our analysis we made a distinction between PD patients without (a history of) depression (PD-MDD) and PD patients with comorbid (concurrent or lifetime) depressive disorder (PD+MDD). Reasons for this comparison are twofold. First the observation of van Praag (1998) that certain biological features of depression persist in times of remission, and secondly the findings by Verburg et al. (1998) that a subgroup of depressed PD patients react to the CO₂ provocation with increased anxiety symptoms when compared to nondepressed PD patients. We

hypothesize that the CO₂ challenge will induce aggression and depressive symptoms in only those PD patients with current or lifetime MDD.

METHODS

Subjects

Subjects were recruited at the Academic Anxiety Center Maastricht, the Netherlands, an outpatient clinic specialized in anxiety disorders. All patients were evaluated by means of a clinical psychiatric interview with special emphasis on anxiety and affective spectrum symptoms, and the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998), a semi-structured psychiatric interview based on DSM-IV criteria (APA, 1994). The diagnosis was confirmed by two experienced psychiatrists. Additionally, patients had a physical examination and routine blood tests. Those patients that met DSM-IV criteria for PD (with or without agoraphobia), were informed about the experimental intervention and were invited to participate in the study. All participating patients gave informed consent. The study was approved by the Investigation Review Board of the University of Maastricht and was conducted according to the declaration of Helsinki. Patients with other axis I diagnoses were excluded, except for comorbid major depressive disorder (MDD), current or lifetime. Patients who were currently using benzodiazepines or antidepressant medication, and patients with physical conditions that could be compromised by the challenge were also excluded like those with cardiovascular or pulmonary disease, epilepsy, pregnancy or a known cerebral aneurysm.

Twenty-five PD patients were included in this study. Nine out of these 25 patients (36%) met criteria for a comorbid lifetime depressive disorder (PD+MDD). Five out of these 9 subjects had a current depression. Nine patients were men, (one in the comorbid group), 16 were women (8 PD and 8 PD+MDD). The sex distribution among PD with and without depression was not significantly different (Chi-square 3.78; $P=0.09$).

Mean age of the PD+MDD patients was 36.3 (SD 7.0) years, mean age of the PD patients without depression 43.6 (SD 10.2) years. This difference was not statistically significant ($t = 1.88$; $df 23$; $P = 0.07$).

Intervention

The experimental intervention was the CO₂ inhalation method, which is described in detail elsewhere (Griez et al., 1987; Verburg et al., 1998). This procedure consists of the inhalation of a single breath gas mixture of 35% CO₂ and 65% O₂.

Assessments

At baseline, just before the CO₂ inhalation, patients were asked to fill in the Panic Symptom List (PSL). This is a self-report scale consisting of 13 items, reflecting the 13 DSM-IV panic symptoms. They are scored on a 0 (not present at all) to 4 (very much present) scale. This scale has been used previously to assess experimental anxiety (Verburg et al., 1995; Schruers et al., 2000).

Patients were also requested to fill in the adapted short Profile of Mood States (POMS) on Aggression (POMS-Ag) and on Depression (POMS-D). The original POMS (McNair et al., 1971) consists of 65 items on 6 affective dimensions, and has been adapted and shortened several times afterwards. For the present study we followed Terry et al. (1999), who selected 7 items from the category Depression (i.e. unhappy, miserable, depressed, downhearted, sad, gloomy and lonely) and 7 items on Aggression (i.e. angry, bitter, annoyed, bad-tempered, furious, spiteful and ready to fight) in order to simplify the task for the subjects and shorten the time needed to complete the experimental procedures. Each item must be scored on a scale from 0 to 4.

The other scales to be scored were a visual analogue scale (VAS) on Anxiety (VAS-A), Aggression (VAS-Ag) and Depression (VAS-D). For the VAS, subjects were asked to point out how they feel at that moment, regarding anxiety, aggression, or depression on a scale from 0 (not at all) to 100 (the worst possible).

All these assessments were repeated directly after the CO₂ challenge.

The occurrence of a panic attack was defined experimentally as an increase of at least 25% on the VAS-Anxiety and any increase on at least 4 PSL-symptoms (Klaassen et al., 1998).

Statistical analysis

Data were analyzed with the statistical software program SPSS for Windows, version 11.0. Student's *t*-test was used to test mean age differences. Sex distribution was tested with the Chi-square test. Nonparametric tests were applied to the assessments of the affective symptoms, due to non-normal distribution of the data. The Wilcoxon-test for paired samples was used to test within group effects, between groups differences were tested with the Mann-Whitney U test for unrelated samples. Significance-levels were set at $p < 0.05$.

RESULTS

Eight of the 16 PD-MDD (50%) and 7 out of 9 PD+MDD patients (78%) had a provoked panic attack (Chi-square 1.82; NS). After the CO₂ inhalation, differences were observed between the PD patient groups with and without depression on all assessments (Table 1).

The post-CO₂ scores on the VAS-Anxiety ($p=0.05$), VAS-Aggression ($p=0.05$) and VAS-Depression ($p=0.01$), and on the POMS-Aggression ($p=0.01$) and POMS-Depression ($p=0.02$) were significantly higher for the PD+MDD group compared to PD without depression. Regarding the (specific) panic symptoms, as assessed by the PSL, the scores were higher for the depressed subgroup, though not statistically significant.

Both subgroups showed a significant increase for the anxiety symptoms assessed by PSL and VAS-A. PD-MDD patients failed to show an increase on aggression parameters, or on the VAS-Depression. The POMS Depression however did increase after the challenge. The PD+MDD group did show an increase on anxiety measures and significant increases on both depression measures and the POMS aggression, but the increase was not statistically significant for the VAS-Aggression ($p=0.068$) (Table 1).

The increase on both aggression scales (VAS-Aggression and POMS-Aggression) and depression scales (VAS-Depression and POMS-Depression) was significantly higher in the PD+MDD patients compared to the PD-MDD group. Table 2 shows the effect of the CO₂ challenge compared for both groups (delta scores: post- CO₂ minus pre- CO₂). The increases on the PSL and VAS-Anxiety were higher for the PD+MDD patient group, but failed to reach statistical significance (Mean $\pm$ SD for depressed on delta PSL 18.2 ± 11.1 versus 9.9 ± 6.6 for nondepressed PD patients, and 53.1 ± 31.0 on delta VAS-Anxiety for depressed versus 28.7 ± 23.1 for nondepressed). Figures 1 and 2 illustrate the differential increase after the CO₂ challenge for PD-MDD and PD+MDD patients.

Figure 1. Increase in VAS Anxiety, Depression and Aggression for PD and PD+MDD patients after CO₂ challenge

Figure 2. Increase in POMS Aggression and POMS Depression for PD and PD+MDD patients after CO₂ challenge

DISCUSSION

Inhalation of 35% CO₂ is capable of inducing a broad spectrum of affective symptoms. In this study the effects ranged from anxiety to aggressive and depressive symptoms, and were most pronounced in the PD+MDD group. The 35% CO₂ challenge appeared to induce more affects (anxiety and aggression and depression versus anxiety only) and also induces stronger affects in the depressed PD subgroup.

On the dimensions anxiety, aggression and depression separately, lifetime depressed PD patients were more affected than PD patients that never met criteria for depression. Thus, lifetime depressed PD patients (even in the absence of current depression) can be considered more vulnerable to a CO₂ challenge than their nondepressed counterparts.

This is the first study that assessed other symptoms than anxiety after CO₂ challenge in PD patients. Some studies used the challenge paradigm to assess PD patients with and without comorbid depressive disorder. However, they all are restricted to anxiety symptoms for outcome measures. Concerning the dimension of anxiety, Verburg et al. (1998) reported a bigger CO₂ challenge effect on anxiety symptoms in a depressive subgroup of PD patients compared with nondepressed PD patients. The present study confirmed this finding; it showed a higher increase on the anxiety measures for the PD+MDD group. In addition, we found a difference on the other affective dimensions of depression and aggression. Our results are in line with the observation that comorbidly depressed PD patients are more severely affected by the CO₂ challenge than the nondepressed PD patients.

In another related study (Targum, 1990) four groups were compared. PD patients without MDD, MDD with a history of PD, MDD without panic, and healthy controls were compared. The study uses a challenge with lactate and one with the serotonergic agent fenfluramine. Lactate has been shown to be panicogenic; fenfluramine has shown to be anxiogenic in PD patients. This study reported that with lactate, the PD patient group, as well as the MDD+PD, revealed a greater anxiogenic response than the MDD patients without panic attacks or healthy controls. With fenfluramine, patients with PD showed a more robust anxiogenic response than the MDD with PD history-group, suggesting a 'protective' effect of the MDD. Their conclusion is towards a distinct neurobiological diathesis in the group of patients who are predisposed to panic attacks, which persist in times of remission. However, the MDD with PD history group is not completely comparable to our PD with depression group because the index disorder differs. Also, our results with CO₂, point in another direction: with PD as the index disorder, a comorbid depression predisposes to an even stronger vulnerability to the panicogenic challenge, whereas Targum found some protection of comorbid MDD+PD for

the fenfluramine condition. Certainly we must be very cautious in comparing findings from different provocation methods.

The role of depressive disorder in this respect is not clear. It has been shown before that ventilation in MDD patients even decreases after a CO₂ challenge (Shershow et al., 1976; Damas-Mora et al., 1978), whereas in PD patients there is an increased ventilatory response (Gorman et al., 2001). This physiological reaction is paralleled by a lower increase in heart rate following a hyperventilation challenge in MDD patients compared with PD and MDD with panic attacks (Nardi et al., 2001). This mild physiological reaction is also reflected in the lack of psychological distress to this hyperventilation challenge, for it did not result in an increase of subjective units of discomfort sensations (SUDS, comparable to our VAS assessment) in MDD patients. Also Perna et al. (1995) have shown that patients with a depressive disorder (without panic attacks or PD) are not vulnerable to this provocation method by means of a CO₂ challenge, but react as normal healthy controls to a CO₂ challenge, when measuring panic and anxiety symptoms. Unfortunately, we have no data on the other affective dimensions of aggression and depression. Neither Perna et al. (1995), nor Verburg et al. (1998) did assess these affects.

From the above data, we could infer that the MDD patients react to a panicogenic challenge in one way, PD patients in another, and in patients where both disorders are present we see yet a distinct reaction. Where both disorders are present, MDD does not protect against the challenge, but the PD seems to determine the response. All this goes against the presence of a common underlying susceptibility.

The present study showed that the 35% CO₂ challenge affects more those PD patients who have ever suffered from a depression, suggesting that one needs to have experienced these affects in real life to be able to re-experience them in the laboratory, or conversely, the challenge may point to a vulnerability which is present. This common vulnerability may be triggered 'by spread' and affect aggressive and depressive feelings in addition to anxiety, but only seems to occur in vulnerable individuals.

Serotonergic dysfunction has been associated with psychopathological dimensions of anxiety, depressed mood, impulsivity, suicide and violence (Apter et al., 1990). Disturbances of aggression regulation are a frequent component of mood disorders, anger attacks have been observed in 30%-40% of depressive disorder (Fava, 1998; Fava et al., 1993; Rosenbaum et al., 1993). Anger attacks also have been proposed as a variant of panic attacks (Korn et al., 1997; Fava et al., 1998; George et al., 1989). Van Praag (1998, 2001) has proposed, and substantiated with psychopathological and biological data, a subgroup of depressive syndromes, that are especially linked to a dysfunctional serotonergic system and whose primary symptoms can be found in the anxiety and aggression cluster, with subsequent depression. These so called 5-HT-

related, anxiety/aggression- driven depressions are supposedly precipitated by stressors in individuals who are susceptible to the psychologically disrupting effects of psychotraumatic events. Our experimental findings very nicely fit in this hypothesis of a specific subgroup of patients who are vulnerable to panic anxiety and depression, as well as experimentally provoked to feelings of aggression (van Praag, 1998, 2001). This holds especially true since van Praag also describes the observation that the 5-HT disturbances persist in times of remission. Our subgroup of lifetime depressive subjects showed CO₂ vulnerability (concerning anxiety, aggression and depression symptoms) in currently non-depressive states, similar like currently depressives did. Studies within the experimental paradigm of tryptophan-depletion (TD) have shown that this method also can evoke symptoms of depressive disorder in subjects who are remitted from MDD (van der Does, 2001). In PD patients the effects of TD alone are not especially panicogenic (van der Does, 2001), but tryptophan depletion may interplay with the 35% CO₂ challenge, in that TD augments the reaction to a CO₂ challenge (Griez and Schruers, 1998; Schruers et al., 2000).

With respect to these observations the neurotransmitter system of 5-HT seems to play a major role. On the other hand, these mechanisms always involve several systems and interrelations, interactions and relative balances. As in depression, where noradrenergic as well as serotonergic influences are known, this probably is the case for anxiety disorders as well, but also for the individual psychopathological dimensions like aggression (Kahn et al., 1988).

Also, separate from the neurobiological perspective, from a more general and historical perspective, anxiety, depression and aggression have all been linked for a long time by psychopathology and epidemiology. Historically, the frequent co-occurrence of anxiety and other affective symptoms and syndromes has led to many philosophical reflections (Himmelhoch et al., 2001). One could say that phenomenology and psychiatric nosology don't always match that well.

From these perspectives, it is not at all so surprising that these related symptoms could be provoked by a challenge test. On the other hand these tests, especially the CO₂ challenge, have been shown to be syndrome-specific i.e. for PD. If then, in a subgroup of comorbid patients, this supposedly specific provocation method gives rise to less specific symptoms like aggression and depression, must we again question the validity of our current psychiatric nosology.

This study just unveils for the first time that a panic challenge may be depressogenic and aggressogenic as well. Some limitations of the present study must be mentioned. The lack of a control group of depressed patients without PD makes it uncertain if a CO₂ challenge can induce aggressive and/or depressive feelings in this specific subgroup. Also, a control group of healthy

subjects should be included to control for affective symptoms that could be raised by a CO₂ challenge. It is known that the CO₂ challenge does not induce anxiety symptoms in depressive patients, but it is unknown if the same applies to the other affective symptoms of aggression and depression.

Another limitation of this study is the small sample of comorbidly depressed PD patients. A larger group would have enabled to analyze possible differential effects of the CO₂ challenge in the subgroups. It would be interesting to look at the effect of a lifetime depressive episode (in PD patients) as a trait marker that can induce a lasting vulnerability to the experimental provocation of depressive and aggressive symptoms by means of a CO₂ challenge. Future studies using the CO₂ challenge paradigm should include these broader assessments of affective spectrum symptoms in addition to anxiety. A future study should assess the effect of a CO₂ challenge in *pure* MDD patients (present and lifetime in separate groups) on the dimensions of aggression and depression. Another study should move to a closer investigation of broader affective symptoms after a panic challenge in pure PD patients, in comparison to comorbid PD patients.

Table 1. Baseline and post-challenge scores on affective symptoms

Scale	Baseline		Mann-Whitney U <i>p</i>	Post challenge		Mann-Whitney U <i>p</i>
	PD (Mean ±SD)	PD + MDD (Mean ±SD)		PD (Mean ±SD)	PD + MDD (Mean ±SD)	
PSL	3.2 (±4.0)	2.8 (±4.7)	NS	13.1 (±7.8)	21.0 (±13.4)	NS
VAS Anxiety	9.7 (±11.4)	9.8 (±16.7)	NS	38.4 (±26.6)	62.9 (±36.6)	0.05
VAS Depression	6.0 (±12.1)	15.0 (±26.1)	NS	8.3 (±17.9)	49.0 (±41.2)	0.01
VAS Aggression	0.3 (±0.8)	10.6 (±23.5)	NS	0.2 (±0.6)	37.6 (±44.8)	0.05
POMS Depression	2.8 (±4.1)	4.8 (±7.2)	NS	5.4 (±5.2)	14.2 (±9.7)	0.02
POMS Aggression	0.3 (±0.8)	2.9 (±5.2)	NS	1.2 (±2.2)	9.1 (±7.7)	0.01

Table 2. Mean increase (± SD) after CO₂ challenge for PD and PD+MDD patients, and within and between groups effects

Scale	PD		Wilcoxon (within group) <i>p</i>		Wilcoxon (within group) <i>p</i>		Mann-Whitney U (between groups) <i>p</i>	
	PD	PD + MDD						
Delta PSL	9.9 (± 6.6)	18.2 (± 11.1)	0.000	0.008	NS	NS		
Delta VAS Anxiety	28.7 (± 23.1)	53.1 (± 31.0)	0.001	0.008	NS	NS		
Delta VAS Depression	-0.1 (± 0.6)	27.0 (±38.3)	NS	0.068	0.02	0.02		
Delta VAS Aggression	2.3 (± 16.2)	34.0 (± 39.3)	NS	0.043	0.04	0.04		
Delta POMS Depression	0.9 (± 2.2)	6.2 (± 6.3)	NS	0.021	0.02	0.02		
Delta POMS Aggression	2.6 (± 4.7)	9.4 (± 6.3)	0.032	0.012	0.01	0.01		

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*Section IV. The interface:
Another approach*

9. THE INTERFACE BETWEEN DEPRESSION AND ANXIETY: COMORBIDITY AND CONCEPTS

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INTRODUCTION

The debate on comorbidity between anxiety and depression leans heavily on current nosography. The vast majority, if not all studies describe the co-occurrence of different disorders along the lines of the two main classificatory systems, the successive versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association), and the International Classification of Diseases and Related Health Problems (ICD, World Health Organization).

As they are defined in the DSM and ICD, depressive and anxiety disorders obviously share a number of clinical features, as well as, most probably, the explanatory pathways to these features. However, for all the accumulated knowledge on the epidemiology and neurobiology of affective disorders, the issue of splitting or lumping together remains largely unresolved. The co-occurrence of anxiety and depressive disorders has led to hypotheses about a common etiology, and several models have been suggested to explain associations between anxiety and depression (Frances et al., 1992). Roughly summarized, these models represent either a unitarian view (lumping the disorders together into one ‘affective’ spectrum) or a separatist view (splitting the spectrum), with various variants in between (Nemeroff, 2002). Another possibility that deserves attention is the ‘artifactual’ argument, that presupposes that the problem of comorbidity is inherent to our imperfect current classification systems, which are based on rather arbitrarily defined criteria and thresholds, using strange combinations of various symptoms and featuring a considerable amount of definitional overlap. In consideration hereof, it may be improper to speak of ‘comorbidity’ in its true sense, the diagnostic framework itself having a deficient validity. Obviously, the way we conceive of psychiatric illnesses, and the constructs we use to describe and classify them, determine the way we explain associations between them. Some of these problems and the nosological challenge they create, are elaborated upon by van Praag (in press).

The present chapter represents a different approach to the relationship between depressive and anxiety disorders. It departs from the traditional appraisal of comorbidity in the current psychiatric literature and largely leaves aside the debate whether DSM/ICD diagnoses are valid or not. A brief look at the assessment methods, and a review of the disparate results they yielded so far in the study of co-existing depression and anxiety has lead us to reflect on the concepts themselves, and the logical relationships that may follow from their meaning. Accordingly, we first discuss a range of clinical scales relevant to our subject: they illustrate the various ways how depression and anxiety have

been conceived of before the introduction of current classifications. To our concern, in general, the use of standardized depression and anxiety scales has been limited to assess progress in treatment studies. Despite their potential usefulness in collecting information on features of emotions like anxiety/fear and depression/sadness, they remain underexploited to assess these effects. To our knowledge, no major comorbidity study has yet been conducted that used classical depression and anxiety scales as a main assessment tool. Thus, while emphasizing the potential interest of assessing depression and anxiety at a very symptomatic level, we are left with comorbidity data from traditional epidemiology. As a result of this, the next part of this chapter can do no better than to summarize a number of major epidemiological surveys, the DSM/ICD framework taken for granted. After all, for purposes of communication, we need a descriptive instrument to provide an overview of the evidence. The last part goes beyond empirical data and offers a reflection on the interface between anxiety and depression from a different perspective, by conducting a concise inquiry into the basic concepts of emotions, sadness and anxiety in particular.

CLINICAL CONCEPTS OF DEPRESSION AND ANXIETY

The way we assess and classify a condition reflects the way we conceive of it. Many quantitative instruments have been developed to assess depression and anxiety, and they cover a broad range of symptoms. It has been assumed that they do not represent diagnostic instruments, but add a quantifiable description of illness severity and profile of symptoms to an existing diagnosis. Because scales themselves can not do anything but assessing -severity of- symptoms, they can be considered as a more sensitive tool to evaluate the details of a clinical condition than the diagnostic interviews, which are aimed by definition at solving a dichotomy (diagnosis versus no diagnosis) on basis of some -rather arbitrarily- predefined criteria. Despite the claim that classification systems are a-theoretical, they can not, simply because behind each description some form of a-priori framework is present. Paying attention to rating scales represents a plea for a return to the basics of descriptive psychopathology. Such a coming back could make sense in further studies on the meaning of basic concepts as depression and anxiety. It is unfortunate that clinical scales have hardly been used in large population surveys. Although they serve no classificatory purpose, their analysis might add worthwhile information on the relative weight of individual symptoms in different conditions of depression and anxiety, their co-occurrence and the total profile of symptoms in distinct disorders.

It is not our intention to enter a detailed methodological discussion on rating scales, neither to discuss nor comment on all individual scales. Suffice it to

mention some representatives of the depression and anxiety scales, and discuss some general aspects relevant to the subject.

The assessment of depression

Amongst the most widely used instruments to assess depressive states at a symptomatic level are the *Hamilton Rating Scale for Depression* (HRSD, also abbreviated as HAM-D, Hamilton, 1960, 1967); the *Beck Depression Inventory* (BDI, Beck et al., 1961); the *Montgomery-Åsberg Depression Rating Scale* (MADRS, Montgomery and Åsberg, 1979) and the *Zung Self-rating Depression Scale* (SDS, Zung, 1965). With many other scales, they differ in various aspects as number of items, nature of items covered, and time needed for completion. Of course, there are also differences between them in validity, reliability and sensitivity. Scales are usually divided in two main categories, the self-rating ('subjective') scales and the clinician-rated ('objective') scales, each category having its own advantages and disadvantages. Faravelli et al. (1986) compared a number of depression rating scales, and showed that one difference between self rating and observer rated scales was that the self rating scales showed more rightward asymmetry (higher severity) and observer rated depression scales tended towards a leftward asymmetry (lesser severity). Moreover, the internal structure of the depression scales, as tested by means of factor analysis, showed considerable differences. Also, the reciprocal correlations between the rating scales are reasonably homogenous, but not particularly high. In the various scales only a subset of items is dedicated to the core symptoms of depression, the other items being apparently dedicated to a variety of accessory symptoms concerning somatic issues, anxiety, or sleep.

In a more recent study Faravelli et al. (1996) analyzed the merits of clinical scales in measuring the severity of depression. They showed that it is not so much the number of symptoms that determines the severity, but rather the presence of certain symptoms, especially those in the melancholic cluster. Different symptoms had different weights in establishing the gradient of severity. In passing, we note that Faravelli and coworkers' observations may be of relevance to our subject. If severity of depression is reflected more in the presence of some core (especially melancholic) symptoms, than in the number of symptoms present, we might infer that at some point there is a change in the quality of the affective state when severity increases. However, which symptoms exactly are concerned, and at which degree of severity is difficult to determine. Scales greatly differ in the number of items devoted to particular core symptoms. Future studies addressing this issue should therefore take into account that information should only be inferred from the appraisal of individual items on these scales. The issue remains largely underexplored.

Another problem worth noting is that, particularly for a descriptive purpose, the total score on a scale does not give any indication as to what specific kind

of items or clusters of items are important for an individual case. It should be kept in mind that when a broad range of symptoms is covered by a scale (Snaith, 1993), many patterns of response may lead to the same score.

The assessment of anxiety

Anxiety scales share the same pitfalls as depression scales, as emphasized in Keedwell and Snaith's review (1996). Even more than is the case with depression, the construct of 'anxiety' is far from unitary, with its repercussion on the validity of the concept as designating a single or complex affective state. Also, the term anxiety covers a different range of phenomena that is bound to language and culture. Constructs as depression and anxiety, refer to states that may fluctuate over time, displaying broad variations in severity from day to day, even within hours.

The *Hamilton Anxiety Scale* (HAS, also abbreviated as HAM-A, Hamilton, 1959); the *State-Trait Anxiety Scale* (STAI, Spielberger et al., 1977); and the *Clinical Anxiety Scale* (CAS, Snaith et al., 1982) are some of the frequently used scales that measure non-specific anxiety.

Large differences have been shown in the emphasis on the various symptom-categories that items can be divided in, like features of anxious mood, anxious cognition, anxiety-bound behavior (avoidance), overarousal, somatic signs, and others (Himmelhoch et al., 2001).

It is worth noting that there are many more scales for anxiety than for depression. Traditional psychiatric nosography clearly distinguishes different types of anxiety disorders. Accordingly, besides 'general' scales covering anxiety as one single concept, other scales are specifically directed at the assessment of particular types of anxiety such as panic/agoraphobia (e.g. the Panic and Agoraphobia Scale, PAS, Bandelow, 1995), social anxiety (Liebowitz' social anxiety scale, 1987) and obsessive compulsive anxiety (e.g. Maudsley Obsessional Compulsive Inventory, MOCI, Hodgson and Rachman, 1977). This again underscores the complex reality that underlies the term of anxiety.

Differentiating depression and anxiety

Special mention should be made of the *Hospital Anxiety and Depression Scale* (Zigmond and Snaith 1983, HADS). This instrument has been constructed for use in general (somatic) hospital settings. The authors took special care to diminish the interference of physical symptoms, which was an important objection against the HRSD. Additionally, they tried to disentangle the constructs of depression and anxiety. Another focus was upon anhedonia, which was considered to be the most reliable clinical marker of likely response to antidepressant drugs. The HADS has been widely used in clinical settings in various countries, is quite easy to complete (containing 14 items) and well

accepted by patients. It has been shown to have acceptable validity and reliability (Herrmann, 1997).

It is remarkable that most scales, that are meant to assess either depressive or anxiety states, contain items obviously related to symptoms of both anxiety and depression. As a consequence, it is risky to differentiate states of anxiety and depression by comparing total scores, even though the scales are supposed to be specific. Bramley et al. (1988) correlated several self rating scales for either depression or anxiety with two criterion observer rated scales (the CAS for anxiety and the MADRS-Modified -this is the MADRS without the items on inner tension and reduced sleep- for depression). Their results showed that self rating scales for depression could discriminate between depressive and anxiety states, but anxiety scales did not. This conclusion also applied to the criterion scales of anxiety (CAS) and depression (MADRS-Modified). An earlier comparative study by Snaith and Taylor (1985) had reached the same conclusion.

A provisory comment on the issue of clinical rating scales is that caution should be exercised when using them in differentiating depression from anxiety on basis of the global quantification they yield as an end score. On the other hand, scales offer an interesting approach of clinical psychopathology, which, if used in conjunction with current classification systems, may add useful information at a descriptive level and challenge some taken-for-granted aspects of our present views.

Classification of depression and anxiety

The history of anxiety and depression throughout the development of the DSM and ICD systems is complicated. For an extensive historical overview of the relationship between anxiety disorders and mood disorders we refer to Himmelhoch et al., (2001), and Glas (2003). In DSM I and II (1952; 1968) clear distinctions between anxiety and depression were not yet made (Levine et al., 2001). The disorders were more drawn apart from DSM-III (1980) onwards, especially where DSM-III was designed to be an a-theoretical, symptom-oriented classification. It stated explicit criteria for inclusion and exclusion, and set thresholds for the various disorders. Diagnosing any anxiety disorder in the presence of a comorbid mood disorder was not allowed, major depression always took precedence. This position is actually very interesting from the conceptual point of view, as it attributes a more central role to the emotion of depression than anxiety. We will revisit this point in the final section of our chapter. Many authors challenged the validity of the hierarchical and exclusionary relationship between anxiety and mood disorders, and in the later DSM-III-R (1987) and DSM-IV (1994) this restriction on axis I was lifted,

tolerating diagnosing separate co-existing disorders on axis I. From then on, many epidemiological studies showed the frequent comorbidity of separately predefined disorders. The clinical reality that did not tally with the categorical views on mental pathology was again 'explained' (van Praag, 1996).

Clinical interviews have been developed within the framework of these systems, to reach diagnoses on basis of predefined criteria. Frequently used standardized instruments are for example the *Structured Clinical Interview for DSM- disorders* (SCID; Spitzer et al, 1992); the *Diagnostic Interview Schedule* (DIS; Robins et al., 1981); the *Composite International Diagnostic Interview* (CIDI; Robins et al, 1987) and the *Schedules for Clinical Assessment in Neuropsychiatry* (SCAN; Wing et al., 1990). The *Mini International Neuropsychiatric Interview* (MINI, Sheehan et al., 1998) is a more recently developed tool for both DSM and ICD diagnoses, and is relatively easy to administer as it takes about 15 minutes to complete. The MINI is increasingly accepted and used for the assessment of psychiatric disorders or screening purposes in epidemiological studies. All have been described in detail elsewhere (Burke et al., 1990; Arbabzadeh-Bouchez and Lepine, 2003). These (semi-) structured interviews often are used in addition to an unstructured interview, to assure that a broad spectrum of disorders has been covered.

The above instruments do not only vary in diagnostic coverage and classification framework they depart from, also the timeframe considered differs.

This summary illustrates the arbitrary way we currently conceive of depression and anxiety, using the tools at our disposal, whether they are rating scales or sophisticated standardized interviews. The collection of the empirical data that appear below is inevitably endowed with the deficient validity of the existent frameworks. Therefore they should be interpreted with caution, and with the appropriate amount of critical judgment they are calling for.

AT THE INTERFACE: PREVALENCE OF COMORBID CONDITIONS

Prevalence figures of comorbidity vary, partly due to a lack of clear conceptualization and definition of the term comorbidity (Wittchen, 1996). Also methodological differences regarding assessment instruments, time frame covered (lifetime or concurrent, past month, 6 or 12 months), case definition (diagnostic criteria or sub threshold conditions included), use of expert or lay-interviewers contribute to uncertainty and confusion (Wittchen et al., 2001). Different types of anxiety disorder show different comorbidity figures with depression, and different types of mood disorders show different comorbidity figures with the separate anxiety disorders. Comorbidity-prevalence rates from

population based, primary care or clinical samples also differ according to the setting that the figures are derived from.

Population surveys

The two largest, and most frequently cited epidemiological surveys stem from the USA. The Epidemiologic Catchment Area (ECA) study was performed among 20,291 subjects from 5 sites within the US, aged 18 years and up (Regier et al., 1990). The ECA used the DIS for DSM-III diagnoses, and worked with lay interviewers. The National Comorbidity Survey (NCS) was developed as the continuation of the ECA and especially addressed the comorbidity of psychiatric disorders. This survey comprised 8,098 subjects from age 15 to 54 years (Kessler et al., 1994). The NCS used an adapted version of the CIDI for screening, and lay interviewers. It also used a more intensive memory enhancement strategy, and found a considerably higher rate of lifetime disorders. The NCS unfortunately did not include diagnosis of OCD. A rough overview of estimated comorbidity figures is given in table 1.

Table 1. Estimates of lifetime comorbidity between anxiety disorders and MDD. After Kaufman and Charney (2000) and Levine et al. (2001).

<i>Diagnosis</i>	<i>Anxiety disorder comorbid with MDD</i>	<i>MDD comorbid with anxiety disorder</i>
Panic Disorder	40-60%	10-30%
Social Phobia	20-35%	30%
Generalized Anxiety Disorder	60%	20%
Post Traumatic Stress Disorder	30-40%	20%
Obsessive Compulsive Disorder	30-60%	
Any Anxiety Disorder	40%	60%

Data from the ECA study on anxiety disorders and comorbidity with mood (and addictive) disorders are reported by Regier et al. (1998). Lifetime prevalence of (any) anxiety disorder was 14.6% and prevalence of mood disorders was 8.3% of respondents. A comorbid anxiety disorder was present in 47.2% of people with lifetime depression.

NCS data were reported by Kessler et al. (1994, 1996), and revealed on the individual diagnostic categories that 24.9% of respondents had one or more anxiety disorder lifetime, a lifetime (any) mood disorder was prevalent in 19.3%, and major depression (MDD) in 14.9% of the population. One-year prevalence rate for anxiety disorder was 17% and for depression 10%. Comorbidity figures from the NCS report that 51.2% of subjects with MDD had an anxiety disorder in the same 12-month period. Of the subjects with lifetime depression, 58% had any anxiety disorder lifetime, 74% had at least one comorbid 'any' psychiatric disorder. The prevalence of MDD figures from

the ECA are lower than the NCS figures, according to Kessler this is due to sampling and ascertainment problems in ECA that led to underestimation of prevalence. Whereas mostly anxiety disorders are shown to be the primary disorder and the MDD secondary, it is an important result from the analysis of the NCS data that this specific association also gives rise to a more persistent course of the depression, and more interference with activities of daily life, suicide and hospitalization for depression (Kessler et al., 1996).

An overview by Kaufman and Charney (2000) demonstrated that about 30-40% of anxiety disorder patients (OCD not included) had a comorbid MDD, with different figures for the individual disorders. Panic Disorder and Generalized Anxiety Disorder have a comorbidity rate of about 65%, Post-Traumatic Stress Disorder 40%, and Social Phobia about 20%. With MDD as the index disorder, a mean comorbidity rate with anxiety disorders is 20%, the highest figure for the Social Phobia 27%, the lowest for Panic Disorder 10%. Most frequently the anxiety disorder (social phobia, GAD and PTSD) precedes the MDD; PD equally frequent precedes, follows, or starts simultaneously with the MDD episode.

Levine et al. (2001) summarized that the whole group of anxiety disorders (including OCD) show comorbid lifetime major depression in about 40%. The individual anxiety disorders show some variation around this figure. GAD is in about 60% of cases seen with comorbid lifetime depression, PD in 40 to 50%, 30% of the OCD patients has a lifetime comorbid major depression, PTSD patients are in 30-40% of cases seen with depression, and 35% of Social Phobia also suffer from a major lifetime depression.

Starting from the other side, of the patients with major depression, on a lifetime basis about 60% suffer from any additional anxiety disorder. Twenty % of these have a GAD, 30% PD, 30% social phobia.

For GAD extraordinary high comorbidity figures have been reported (Wittchen et al., 1994). Up to 90% of GAD patients have a lifetime comorbid psychiatric disorder, mainly mood disorders like MDD 60% and dysthymia 40%.

Another review by Merikangas et al. (1996), computed data from a set of epidemiologic population based surveys, and concluded that there was a strong and consistent association between the mood disorders and anxiety disorders (and substance abuse); magnitude of comorbidity between mood disorders and anxiety disorders was greater than comorbidity between the affective disorders and substance abuse.

Epidemiological data on a newly DSM-IV proposed diagnosis of Mixed Anxiety Depression (MAD), a syndrome combining features of both anxiety and depression (sub threshold conditions) where neither would qualify as a predominant, stand-alone diagnosis (Zinbarg et al., 1994; Rapaport, 2001;

Barlow and Campbell, 2000), interestingly showed an unexpectedly low prevalence rate of about 1% (Wittchen et al., 2001).

Primary care studies

A large-scale study by the World Health Organization has investigated the prevalence of mental disorders in primary health care, a total of 25916 subjects were screened across 15 different countries (Sartorius et al., 1996; Wittchen et al., 1999; Lecrubier and Ustun, 1998). In the second-stage assessment of 5438 subjects the CIDI was applied. From this study it was shown that 62% of all depressive cases also suffer from another mental health problem, most commonly anxiety disorders. Of the patients with anxiety disorders, 45% had a comorbid depression, of patients with a depression about 40% had an anxiety disorder as well. It was shown that an advantage of comorbidity was that the likelihood of recognition of mental disorders increased, and also the likelihood of receiving treatment was highly increased by the presence of comorbid disorders.

Clinical comorbidity

Many clinical studies have reported on comorbidity between anxiety and mood disorders (Breier et al., 1984; Starcevic et al, 1992; Ball et al., 1995; Davies et al., 1995). Due to space limitations, we focus on some recently published studies. Diagnostic comorbidity rates vary between clinical studies because they are influenced by several methodological factors, amongst others the number and nature of disorders assessed, the method of assessment (semi-structured interview versus clinical evaluation), and time period covered (current versus lifetime).

In a clinical population (Zimmerman et al., 2002) with major depressive disorder (N=479), 64.1% of patients also met criteria for at least one comorbid Axis I disorder, and 36.7% of depressed patients had two or more comorbid disorders. The most frequent comorbid diagnoses belonged to the group of anxiety disorders (56.8%), with social phobia being the most frequent individual disorder. This study also showed that 14% of patients had a current (any) comorbid disorder that was in partial remission. Also, Not-Otherwise-Specified (NOS) categories were rather frequent: 14.6% had any NOS anxiety disorder, especially sub threshold PTSD and sub threshold PD.

Another clinical study from Finland, the Vantaa Depression Study, investigated 269 patients with MDD (Melartin et al., 2002). From this sample, 73% were female, 83% were outpatients. This study covered all DSM-IV axis I and axis II disorders when looking for comorbidity, and used the semi structured SCAN. Most of the patients (79%) had at least one current comorbid diagnosis, and even 52% had two or more comorbid diagnoses. Anxiety disorders were present in 57%, 25% of patients had alcohol abuse or dependence, and 44%

had a personality disorder. The last figure, on comorbid personality disorder, however, could be distorted by the fact that the SCID II was done while the patients were depressed. Nonetheless, the conclusion must be that comorbidity among psychiatric patients with MDD is very common, and often multiple.

Finally, let us mention that these recent results are in line with earlier reports that found high comorbidity rates among MDD patients, like Sanderson et al. (1990) who reported 60% of comorbid axis I disorders, most commonly anxiety disorders. The review by Wetzler and Sanderson (1995) reports a range of 7-61% (mean 24%) of PD patients have a current comorbid depressive disorder, lifetime depression is reported in about 65% of PD patients. Of patients with primary depressive disorder, about 14% (range 9-69% have a comorbid panic disorder, for this group no lifetime data were available.

These prevalence figures apply to the various anxiety disorders and (unipolar) major depression. Several studies have suggested that comorbidity rates for the affective disorder subgroups differ. As was concluded in a review by Freeman et al. (2002), as well epidemiological studies as clinical studies have found a high co-occurrence of anxiety disorders with bipolar disorder. OCD has been suggested to show a high comorbidity rate with bipolar disorder (Chen and Dilsaver, 1995a), but results from different studies are not unequivocal (Kruger et al., 1995; Perugi et al., 1997). For the specific relationship of bipolar disorder and Panic Disorder, there seems to be more evidence, from epidemiologic Chen and Dilsaver (1995b) and from several genetic studies (MacKinnon et al., 2002; Rotondo et al., 2002). Likewise, social phobia and PTSD have been associated with bipolar disorder (Freeman et al., 2002).

REFRAMING CONCEPTS

The bulk of above surveys notwithstanding, ICD and DSM frameworks offer no explanation for the link they suggest between anxiety and mood disorders. This is little of a surprise. Both systems largely rely on a surface descriptive approach of clinical constructs, and a good proportion of these constructs suffer from a suspicious validity.

A closer analysis of our basic concepts can make sense here. The definition of concepts determines the logical relationships between them. Clarifying the concepts of depression and anxiety may illuminate their interface.

The remainder of the present chapter is an attempt to pay attention to these issues. Which emotions, which behaviors, which functions of an organism, do the constructs of depression and anxiety exactly refer to? Pathology will be subsumed and clinical categories somewhat de-emphasized. We will consider disturbed emotions, endorsing affectivity as the key feature of anxiety and depressive disorders. We will address the nature of emotions, focusing on

sadness and fear. We assume that there is a close conceptual relationship between sadness and fear and that the logical link between depression and anxiety can be inferred from this proximity. We expect the following considerations to help shedding light on the aggregation of anxiety and depression in the lifespan of some individuals.

ON THE NATURE OF EMOTIONS

The force to exist

In the *Ethics* (1677), a masterpiece of deductive inference, the Dutch philosopher Benedict de Spinoza, questions the nature of human affectivity.

Apparently, Spinoza observes, everything in nature tends to persevere into existence. Inanimate objects simply persist. Living organisms survive: they grow, develop and reproduce. Life appears to be endowed with an appetite for life.

In their striving to be, organisms are driven towards everything that fosters their development, and they refrain from anything that thwarts their force to be. This we observe in unicellular beings approaching the nutriment they need to stay alive and consistently fleeing a drop of acid which threatens their existence. At the other end of complexity humans' struggle for life is more sophisticated. The *Ethics* (III, *prop.* 9) posits that in humans, striving for life is conscious and appetite becomes desire. Beside food, water and warmth, humans tend to pursue other goods as knowledge, wealth, honors and social recognition, to name a few. In contrast, they seek to avoid things as illness, poverty and humiliation. They feel the former category to booster their quality of life, in other words their power to be, and the latter to endanger it. Accordingly, items belonging to the former category are called 'goods', while things in the second category are labeled 'evils' or 'adversity'.

Consciousness of the ability to be

Thus, in humans, appetite for life is a conscious desire which rests both in the body and in the mind. As a consequence, for each change in an individuals' capacity to be there is a concomitant change in his mind. These transitions we call emotions (*Ethics*, III, *prop.* 11). Therefore, emotions are the consciousness of the organisms' own capacity of existence.

This may be either a pleasant or a painful consciousness⁴, depending on whether the 'power to be' is going stronger or weaker. Each change in the organism that strengthens life is sensed as pleasure, and each change that weakens life, as pain. Pleasure is excellence of the mind to the same extent as fitness is excellence of the body. Pain in contrast, is a shrinking of the mind.

⁴Psychologists refer to the positive or negative valence of emotions.

It follows that basically, there are only two emotions, pain and pleasure. Sadness is the prototype of pain and joy the prototype of pleasure. However humans do experience a great diversity of emotions because they tend to associate pain and pleasure with different ideas in various contexts.⁵

Thus emotions essentially are the conscious side of the organism's fitness for survival. Spinoza's fascinating suggestion is consonant with current evolutionary views in affective neuroscience (McGuire et al., 1992; Nesse, 1990, 1999; Damasio, 1995). Emotions are believed to have emerged from ancient brain processes that we, humans have inherited from ancestral species. The function of these homologous brain systems is to energize organisms, helping them to cope with their environment and to maximize their chances of survival. Panksepp (1998) posits that emotional systems "generate an animals' egocentric sense of well-being with regard to the most important natural dimensions of life". Throughout the ages, the primal issues of maintaining one's physical integrity, finding goods and protecting them, breeding, rearing and securing social support for oneself and the youths progressively generated specific coordinated responses. In higher vertebrates, mammals in particular, these capacities turned out to encompass powerful internal feelings sensed as emotions. Panksepp argues that there is reasonable experimental evidence to identify a number of such 'basic emotional systems' in the brain. Panksepp's *Seeking, Fear* and *Panic/Loss* systems are of particular interest for the sake of our inquiry (see table 2).

⁵ "Love is nothing else but pleasure accompanied by the idea of an external cause; hatred is nothing else but pain accompanied by the idea of an external cause. We further see that he who loves necessarily endeavors to have and keep present to him the object of his love, while he who hates endeavors to remote and destroy the object of his hatred" (*Ethics*, III, prop.13).

Table 2. Three main emotional systems corresponding to three major evolutionary challenges as suggested by Panksepp (1998)

	<i>Seeking system</i>	<i>Fear system</i>	<i>Panic-Loss system</i>
<i>Evolutionary challenge</i>	Finding resources (e.g. food, water, sex)	Avoiding harm and destruction	Maintaining social bonds and cohesion
<i>Emotive state, positive valence (fitness)</i>	Desire, strive	(<i>Absence of fear</i>)	Attachment, love, trust
<i>Emotive state, negative valence (unfitness)</i>	(<i>Absence of desire</i>)	Fear, anxiety	Separation, distress, grief, sorrow
<i>Putative brain structures involved</i>	Mesolimbic and mesocortical dopaminergic pathways	Central and lateral amygdala, anterior and medial hypothalamus, periventricular gray	Midbrain periaqueductal gray, ventral septum, dorsomedial thalamus, stria terminalis, cingulate gyrus ¹
			¹ : structures implicated in Distress Vocalizations

Let us quote Panksepp describing the *Seeking* system. “This emotional system is a coherently operating neuronal network that promotes a certain class of survival abilities. This system makes animals intensely interested in exploring their world and leads them to become excited when they are about to get what they desire. It eventually allows animals to find and eagerly anticipate the things they need for survival, including, of course, food, water, warmth and their ultimate evolutionary survival need, sex (...) it helps fill the mind with interest and motivates organisms to move their bodies effortlessly in search of the things they need, crave, and desire. In humans, this may be one of the main brain systems that generate and sustain curiosity, even for intellectual pursuits.” Arguably, there is a conceptual analogy between seeking, sensu Panksepp, and striving to be, sensu Spinoza. But what further about pain, pleasure, and, for the sake of our inquiry, sadness and joy?

SADNESS

Sadness is the painful awareness of a decay in the capacity to keep oneself into existence. Therefore sadness is the consciousness of a loss relative to a previous state. The essence of sadness is the collapse from a higher to a lesser degree of fitness.

There is no emotion in having a particular degree of fitness. The way I am is not a matter of pain or pleasure. The way I am makes me neither happy nor miserable. Pain and pleasure only proceed from a difference in the way I am, compared to the way I was. Emotions are driven by desire, and desire constantly compares. Thus, pleasure and pain are not linked to a specific level of abilities; they are a function of passing to a higher or a lesser degree in the power of existence. Only transitions can trigger emotions⁶.

This explains why emotions are similar in all individuals, regardless of their level of success in coping, survival and self-fulfillment. Pain affects the successful, and the poor feels pleasure. This explains the sad person feeling deprived with no apparent appreciation for the success and the wealth that he or she may still have.

The intimate relationship between the concepts of sadness and loss, has been commandingly conceptualized in Bowlby's attachment theory (1980), and to a lesser extent in Seligman's notion of learned helplessness (1975).

Bowlby's separation-loss theory points to the role of the primal bond between the mother and her offspring, and emphasizes the dramatic consequences of its disruption on the survival abilities of the infant. Abandonment of the vulnerable infant through loss of maternal care bears a relationship to prototypal sadness. One of the most fascinating experimental findings in this regard is the phenomenon of the so-called Distress Vocalizations (DV). Animals, rat pups or young chickens separated from their mother and left alone in a strange place, start emitting very specific, usually ultrasonic vocalizations, seemingly to solicit parent's attention. Following separation, the response often is biphasic, with an early phase attended by many vocalizations, intense motor activity and an active search for the caregiver; this is followed by a phase of despair-like behavior, with progressive extinction of the DVs, prostration and immobility. In line with Bowlby, Panksepp (1998) refers to a single *Panic/Loss/Sorrow* system. Laboratory studies have shown structures of this system to control DVs. Apparently, emotions linked to the *Panic/Loss* system provide safeguards for infant-mother attachment and social bonding. Noteworthy, the *Panic/Loss* system reaches its highest development in the mammals, which are social beings by excellence; separation and abandonment have dramatic, life threatening consequence for newborn mammals (Panksepp, 1998, 2001).

Seligman (1975) developed the concept of learned helplessness, which he related to depressive behaviors. In Seligman's experimental paradigm, animals, most often dogs, were submitted to a series of electric shocks they could neither avoid nor escape. When later presented with similar aversive stimuli,

⁶ "For if man were born with the perfection to which he passes, he would possess the same, without the emotion of pleasure" (*Ethics*, III, *Definition of the Emotions*, III, note).

most animals helplessly underwent the events despite having regained the possibility to escape, in an apparent passive attitude towards forthcoming adversity. Seligman's experiments can be reinterpreted as instances of loss of ability in mastering one's environment. Seligman's dogs had lost the ability to exercise control on environmental parameters that profoundly affected them. Such a loss represents a definite shrinking of the organism's ability to live and survive.

FEAR

Fear is pain in the future

Throughout the Middle Ages scholars used to represent the principal emotions in a 2x2 table (table 3) which scheme actually relied on the doctrine of the ancient Stoics.

Table 3. Basic emotions according to the Stoics

	<i>Present</i>	<i>Future</i>
<i>Goods</i>	Pleasure	Desire
<i>Evils</i>	Sadness	Fear

Humans' appraisal basically distinguishes between good and bad events. Pleasure is the present experience of good things, pain the experience of evils. Regarding the future, humans tend to desire things they believe to be good, and to fear those they believe to be bad. Thus fear is the emotion with a negative valence, pertaining to the future. Fear obviously belongs to the negative emotions, related to evils and associated with pain. Contemporary evolutionary views emphasize this negative valence of fear as a functionality that helps keeping the organism away from adversity. Indeed, avoidance is constitutive of fear. Noteworthy, avoidance as a coping strategy dictated by fear makes sense as long as no irremediable damage has occurred to the organism. Once damage has occurred, it is too late to avoid: there is loss, and actual loss is sadness. Thus fear refers to unaccomplished pain, in other words, pain in the future.

Fear is diverse and the evils a particular organism seeks to avoid, numerous. Accordingly, naming fears has been a much appreciated pastime of earlier psychopathologists (Campbell, 1981). Yet a closer look at the content of highly prevalent fears is more interesting. Phobias typically represent fears of concrete, circumscribed external objects. Evolutionary views on phobias hold that phobic fears are related to innate mechanisms shaped by nature as safeguard for life in a hostile environment (Ohman and Mineka, 2001; Poulton and Menzies, 2002). Animals have been prepared via natural selection to avoid

things that may more or less endanger their survival. Against the background of human psychopathology, Nesse (1990) lists a number of subtypes of anxiety, each of which he tentatively relates to a particular kind of primal danger (table 4).

Table 4. Putative primal dangers related to different types of anxiety according to Nesse (after Nesse, 1990)

<i>Anxiety</i>	<i>Primal danger</i>
Panic	Present vital threat (e.g. attack by a predator)
Agoraphobia	Highly unsafe environment (attack likely)
Social anxiety	Rejection from group membership
Separation anxiety	Social loss and disruption of protective bond
Blood-injury phobia	Blood loss
Hoarding compulsions	Lack of food or other goods
Washing compulsions	Infection
Animal phobias	(Vital) threat by dangerous animals

All fears have pain in common, and pain is the subjective side of a loss in the power to be. Therefore, experiencing pain is facing a loss in one's capacity of survival. For a living being, the ultimate loss is death. Thus, the ultimate fear is a fear of dying, and Epicurius rightly pointed to the fear of death as the core of all human misery (Diogenus Laertius, book IX)⁷. Thus all instances of fear are instances where possibly the organism's very existence is endangered. The case is clear for the prey-predator paradigm, as it is for specific phobias such as fear of heights, enclosed spaces, fire, natural disasters as thunder and storms, sharp objects and animals. In all these situations, the animals' existence is at risk, either acutely (prey-predator) or remotely. Social fears represent a distinct category: they typically apply to higher vertebrates, mammals in particular. Mammals need social support to survive, should it only be for the immaturity of their youths. For social animals, including humans, loss of social integrity may be of vital importance; it is loss of life. This explains social fears in the perspective of an ultimate fear of death⁸.

⁷ However, Epicurius further reasoned that we should not fear death because in fact we never have knowledge of death: as long as we are, death is not, and once death is, we are not any more. In this he may have missed that the painful essence of fear lies in *waiting now* for the future evil, not the evil itself. Even though the object of the fear never materializes, fear hurts.

⁸ From a conceptual point of view, one may argue that social fears occupy a specific place amongst fears. They are more recent in the history of evolution and, compared to archaic safeguards as other phobias, they may be a more pertinent feature for well organized animals, as humans. To a social being as mammals are, the threat of storm or of a small animal may have become less salient than the threat of separation and abandonment. To this extent social fears may have evolved very close to the image of acute loss, death, sadness and depression

In sum, there is nothing else in fear but pain, pain being conceived of as a deficit in the ability to survive.

Fear is uncertain and therefore inconstant

In the *Ethics*, Spinoza conceptualizes of fear as being an inconstant pain. This pain arises from the image of something concerning which we are in doubt. More precisely, the emotion of fear, he further writes, arises from the idea of something past or future, whereof we to a certain extent doubt the issue. Fear pertains to the future, possibly to the past⁹. As far as the object of fear is in the future, to some extent the causality of fear is in the future. Now, the future is not certain. Therefore, uncertainty is constitutive of fear.

Uncertainty relates to unpredictability¹⁰. There has been quite a lot of experimental work on the link between unpredictability and anxiety (Mineka and Kihlstrom, 1978). Typically, an environment that goes unpredictable becomes anxiogenic. In an unpredictable environment cues are not reliable. A typical example in a learning paradigm of classical conditioning occurs when, given the occurrence of the UCS (the signaling event), the probability of occurrence of the CS (the signaled event), equates or approaches the probability of non occurrence of the CS. In such an environment, the danger of loosing control is great. And loosing control on one's environment entails a loss in the organism's ability to face the challenge of survival.

The view of fear as uncertainty may provide a first hint to illuminate its relationship to sadness. Fear is a foreboded loss of control on ones environment. Such a loss of control affects the organism's power to be. Thus fear is a threat of sadness.

Fear is not only uncertain. Fear is also inconstant. Fear is variable and changing over time. Why should we logically expect fear to be an inconstant emotion? The argument may run as follows. The future exists in the subjects' mind as an image only. The same applies to the past. Past and future are kept in existence through images in the mind (Damasio, 1994). However, while facts are irrevocable, images are prone to change. When the subject has in mind an image of doom and loss, he feels painful and tends to substitute that image by a different one. The mind endeavors to repel images of doom and replace them by images of happiness. The individual naturally seeks a glimpse of success

⁹ Fear related to a past event is typically obsessive fear. The obsessive subject doubts about past as much as about future events. To this extent, obsessions are merely a particular case of anxiety. However, we will not further discuss the concept of obsessions in the present demonstration.

¹⁰ Not each instance of uncertainty can be explained by unpredictability. Unpredictability may explain uncertainty only as far as future events are concerned. Unpredictability does not encompass uncertainty pertaining to past events.

rather than failure, a glimpse of joy rather than pain¹¹. Thus there is an inherent instability of fear. The inconstant pain of fear always mixes to some extent with the inconstant pleasure of hope. There is neither fear without hope, nor hope without fear, Spinoza insists.

The view of fear as inconstant emotion may provide us with a second hint concerning the relationship between fear and sadness. Take uncertainty away, and hope becomes pleasure. Take uncertainty away, and fear becomes despair (*Ethics*, III, *prop.* 17). We might expect fear to become sadness when images of doom overtake images of hope in the mind, making fear less inconstant. Fear closes down to sadness as a function of its constancy, in other words to the degree it is turning chronic.

FROM FEAR TO SADNESS

When uncertain sadness turns certain

At first, the mind of the fearful oscillates, expecting the worst but wishing the best. The subject with fear anticipates doom, but endeavours to keep in account that the threat may not materialize.

Then comes exhaustion, and images of doom start dragging on in the mind. Ups and downs in the subjects' mood flatten, giving way to generalized negative expectations in face of adversity¹². The fluctuating fear eventually freezes into a static state with a steady negative valence. The fleeting glimpses of disaster, originally mixed up with hope, merge into the protracted contemplation of a looming pain. Loss is now taken for granted. The *Ethics* emphasizes that if the elements of uncertainty are removed, fear turns into despair (*Ethics*, III, proposition 18). Despair encompasses the certainty of damage.

Painful expectations, lasting injuries that hurt, and a place for panic

In the flow of time, the mind continuously anticipates the future, considers the present and remembers the past. This incessant sequence is the measure of the subject's expectations. The time passing by is the ultimate evidence.

Fear looks forward to an uncertain harm. Sadness reflects on lost excellence. There is an evident temporal relationship between fear and sadness. The object of fear is the future; the object of sadness is the past. Fear and sadness are lasting emotions, extending by essence beyond the time present. Fear waits for the future to materialize; sadness keeps memory of the past.

¹¹ "he who fears, in other words doubts, concerning the issue of something which he hates also conceives something which excludes the existence of the thing in question: to this extent he feels pleasure, and consequently to this extent he hopes that it will turn out as he desires" (*Ethics* III, Definitions of the Emotions, XIII).

¹² Generalized apprehensive expectation: the link between fear and sadness?

In contrast panic is the immediate emotion linked to the assault of unfolding adversity. Panic is the internal experience of the acute threat to the organisms' survival, when its very existence is at stake. It ensues that conceptually, not only fear and sadness are different, but between them there is a logically designated place for the distinct state of panic. This all is consonant with the view that putatively "anxiety prepares the system for an anticipated trauma whereas panic deals with one that is already in progress" (Bouton et al., 2001).

Fear as unfulfilled sadness

The argument developed in the previous paragraphs suggests a number of ideas about the definition of emotions, and, regarding our original concerns, about the nature of sadness and fear. Emotions in general have been related to the drive of life and the striving for survival. They should be regarded as the 'contentment', or the absence thereof, of the organism sensing an increase or a decrease in its chances of coping with life. This satisfaction must be conceived of as an evolutionary concept, having grown from reflex-like approach and avoidance reactions in single-cell beings, to conscious desire and complex, cognitively loaded emotions in humans. At least in higher mammals, fear and sadness are essentially the painful perception of a threat of, or an actual loss in the 'power to be'. Fear, leaning forward to the uncertain future, is intermittent sadness, being mixed up with the hope of escaping danger. Sometimes the fearful subject forebodes a loss, sometimes he hopes for the best. Thus, fear is incipient sadness, which reaches completion when time consumes the anticipated loss. It ensues that there is continuity between fear and sadness in the flow of time. In order to become sadness, fear requires that time passes. The process unfolds in the direction of the arrow of time, and this tells that fear will eventually become sadness, but that sadness is not likely to change into fear.

Anxiety as incomplete depression?

Several arguments arguably illustrate the idea that anxiety is a putative state of unfulfilled depression.

When assessed on the independent dimensions of positive and negative affectivity, patients with anxiety states present increased ratings on both negative and positive affectivity. In contrast, subjects with depression yield high scores on negative affectivity only, having seemingly lost any significant profile of positive affectivity. This shows anxiety and depression to share a common profile, depression representing one further degree yet in psychological pathology (Tellegen, 1985; Clark and Watson, 1991).

Van Praag discusses as plausible the possibility that anxiety induces depression, or at least a subtype of depression. He observes that anxiety symptoms, and anxiety related irritability often precede the development of depression. He

refers to this type of depression as being ‘anxiety/aggression-driven’ and links this construct to serotonergic disturbance (van Praag, in press).

Our analysis presents the passage from anxiety to depression as mediated by a phase of constant and chronic fear. As we have reported earlier in the present chapter GAD, the anxiety disorder which arguably yields the highest degree of chronicity, strikingly shows one of the highest degrees of depressive comorbidity. The close proximity between GAD and depression has even lead some authors to speculate on a common diathesis between both disorders (Kendler et al, 1996; Mineka et al, 1998).

Addressing the cognitive correlates of anxiety and depression, Alloy and coworkers (1990) hypothesize that depression, compared to anxiety, is characterized by a sense of certainty encompassing hopelessness. This idea is perfectly consistent with our above analysis. Waikar and Craske (1997) investigated 329 patients with affective pathology and found support for Alloy and coworkers’ suggestion.

We further infer that time is an essential dimension in the transformation of fear into sadness. We some years ago examined whether chronicity is a factor towards depression in a population of panic disorder (PD) patients. The results not only support the idea, but suggest as well a direct relationship between the severity of PD and the development of subsequent depression (Griez and Overbeek, 1997).

If fear ‘prepares’ for sadness, one should logically expect anxiety with subsequent (lifetime) depression to be more prevalent than depression alone. This is the case (Mineka et al, 1998). Pure depression nevertheless occurs independently, for instance as a result of acute unforeseen loss events, as sudden grief.

In sum, it appears plausible that fear is a logical itinerary to sadness, and that there may be a continuum between clinical conditions of anxiety and depression.

A note on the concepts of fear and sadness in evolutionary perspective

The above account of emotions broadly refers to evolutionary views. There is an extensive literature on evolutionary biology, while evolutionary views in psychiatry and clinical psychology are spreading fast. Yet investigators do not all agree in their interpretations. A number of authors tend to consider emotions in general, regardless of their valence, as being in itself instances of adaptations. Following their view, anxiety and depression have supposedly been ‘invented’ by nature as adaptive responses to the challenges of ancient environments (see for instance: Nesse, 1999, Troisi and McGuire, 2002). Accordingly, they deploy a lot of heuristic efforts to explain the potential virtues of painful conditions as depression and other psychiatric illnesses

(Nesse, 2000). Others have challenged these 'adaptationists' positions. Criticism has been voiced on some methods used in evolutionary psychiatry (McLoughlin, 2002, Lane and Luchins, 1988, Dubrovsky, 2002).

The conceptual analysis in the present chapter is consistent with modern neurosciences (Panksepp, 1998, Damasio, 1994). However, it should be noted that our analysis does not present each emotion as being a blessing of nature in itself. Emotions are the internal sense of wellbeing that corresponds to the capacity for life, or the fitness of the organism. For each increase in fitness there is an emotion with a positive valence, for each decrease, an emotion with a negative valence. Fear and depression are the emotional side of a loss of power for life. Consequently, they express a decrease in fitness. From this point of view, the analogy drawn between anxiety and depression on one hand, cough and fever on the other hand (Nesse, 1999) may be conceptually wrong. Fear and sadness are not the consequence of a loss of life, let aside an adaptive reaction to it; they *are* loss of life and express a lack of fitness. Depressive individuals present hormonal and immunological disturbances, a sign that they are at increased vulnerability (van West et al., in press). Another striking case is the increased prevalence of affective disorders in physically ill subjects, amongst others, cardiac patients Griez et al., 2000; Fleet et al., 2000; Prasure-Smith et al., 1993); in cardiac patients in particular, the occurrence of affective pathology has been associated to a poorer vital prognosis.

EPILOGUE

Our analysis intends to clarify concepts. It does not invalidate or replace empirical research. From a conceptual point of view, there is continuity between fear and sadness but no overlap. The continuity may be consistent with the idea that anxiety and depressive disorders belong to a same spectrum. The absence of overlap however argues against the idea of a diagnostic pleonasm (van Praag, in press). To the extent that fear is not merely sadness, anxiety is no depression. Fear is foreboded sadness, moderated by uncertainty. It is from this point of view that one might argue that anxiety disorders are conceptually less severe than depression.

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SUMMARY AND CONCLUDING REMARKS

The frequent co-occurrence of anxiety disorders with depression in clinical practice provided the foundation for this thesis. Several studies were performed at the *interface* between anxiety disorders and depressive disorders, and related features like suicidality and sleep complaints.

After a *foreword 1* in the *Introductory Section*, *chapter 2* provides an overview of large population based surveys concerning prevalence, demographics, risk factors, natural course, and comorbidity of the DSM-IV anxiety disorders. The estimated lifetime prevalence of all anxiety disorders is 25%, compared to major depression which occurs in about 17% of the population. Among anxiety disorders, social phobia and specific phobias are the most prevalent (11-12%). The prevalence figures for the other anxiety disorders are: panic disorder (PD) 2%, obsessive-compulsive disorder (OCD) 2-3%, generalized anxiety disorder (GAD) 5%, and 7% of the population may develop post-traumatic stress disorder (PTSD). Various factors such as selection bias, severity of symptoms, diagnostic criteria, and instruments used in these studies warrant great caution in interpreting these epidemiological data.

Section I starts the description of the empirical studies with data on comorbidity and treatment aspects of comorbid disorders on the index anxiety disorder. *Chapter 3* reviews the literature on comorbidity of PD and depression. In addition, it reported on a retrospective study in PD patients. Although PD is not the most prevalent anxiety disorder, it is frequently encountered in clinical practice because of its usually disabling consequences. In order to study the clinical characteristics and impact of comorbid depression on treatment outcome, we assessed comorbid depressive features in PD. In a sample of 160 patients with panic disorder, 30% met criteria for concurrent major depression or dysthymia. The group of depressed PD patients were significantly older ($p < 0.05$), and reported more severe anxiety symptoms than the nondepressed PD patients. Both groups benefited equally from combined pharmacological and behavioral treatment, as illustrated by a comparable decrease on the assessment scales used. These findings are consistent with a theoretical model that conceives anxiety disorders (i.e. PD) as predisposing to depression.

Chapter 4 reports on the comorbidity of OCD and depression, and the impact of the comorbid depression on treatment outcome for OCD. A retrospective

study was performed on baseline ratings of 120 OCD patients and posttreatment ratings of 72 patients. One third (37%) of the OCD patients also met DSM-IV criteria for major depression or dysthymia at baseline. Symptom severity of OCD symptoms at baseline did not differ between depressed and nondepressed OCD patients; on general anxiety symptoms the comorbid group was more severely affected. Both depressed and nondepressed OCD patients responded well to treatment, as reflected in assessments for depressive, obsessive-compulsive, and general anxiety symptoms. However, comorbid depression appeared to have a negative effect on treatment: depressed OCD patients showed less improvement than nondepressed OCD patients on most scales. In addition, although both groups were equally affected at baseline, posttreatment scores on OCD measures were significantly higher for the depressed OCD patients than for the nondepressed group. These results underscore the importance of assessing comorbid disorders in OCD, since this may have an impact on treatment outcome.

Section II contains the reports on associated features of panic disorder. *Chapter 5* assesses suicidal ideation and risk for PD patients. In order to assess to what extent a reported rate of higher suicidality in PD could be attributed to PD alone, we excluded all comorbid DSM-III-R axis I or axis II pathology in this study. Fifty patients with *pure* PD (but with or without agoraphobia) were compared with fifty age- and gender- matched controls. We found that *pure* PD patients were more preoccupied with death in general than controls; PD patients also expressed a passive wish to be dead more frequently. However, PD patients did not think about committing suicide more frequently, nor reported more suicide attempts than controls. We concluded that PD alone was not associated with higher suicide risk. By meticulously excluding comorbid disorders in PD, we showed that it is likely that the previously reported higher suicide risk in PD can be accounted for by prevalent comorbid disorders.

Chapter 6 focuses on the association between sleep complaints and PD. The study assessed the prevalence of sleep complaints in PD in comparison with sleep complaints in a normal population, and assessed whether nocturnal panic attacks and comorbid depression could account for sleep complaints in PD. Seventy PD patients and 70 healthy controls were asked about their subjective sleep characteristics by means of the Sleep-Wake Experience List, which assesses sleep/arousal complaints over a 24-hour period, in the past three months. Sixty-seven percent of the PD patients reported sleep complaints, compared to 20% of the controls. Seventy-seven percent of the PD patients with comorbid depression and/or nocturnal panic attacks reported sleep

complaints versus 53% of the *pure* PD patients. We concluded that both nocturnal panic attacks and comorbid depression only partially accounted for the higher prevalence of sleep complaints in PD: also *pure* PD patients without nocturnal panic and without depression suffered more frequently from sleep disturbances than healthy controls.

Chapter 7 describes a study on the predictive value of a specific subscale (Blood-Injury phobia) of the Fear Questionnaire (FQ) for treatment outcome in PD. In 1995 an intriguing finding was reported by Slaap et al. They found that blood-injury phobia scores on the FQ were negatively correlated with drug treatment-outcome in PD. We assessed 61 PD patients by means of a retrospective chart analysis at baseline and after 12 weeks of SSRI-treatment. Response was defined as absence of panic attacks and/or a reduction of at least 50% on the FQ Agoraphobia subscale. Nonresponse was defined as the continued presence of panic attacks. Twenty (32%) patients were found to be nonresponders. Fifty-five percent of the nonresponders had a high score (cutoff = 20) on the FQ Blood-Injury subscale. This was only the case for 19.5% of the responders group ($p=.008$). Like Slaap et al., we concluded that the presence of comorbid blood-injury related phobic symptoms negatively affects treatment for PD and agoraphobia.

Section III concludes a series of clinical studies. *Chapter 8* describes an experimental study using the CO₂ paradigm. To date, CO₂ challenge tests in PD patients focused on anxiety as the sole outcome measure. The aim of this study was to assess affective symptoms in addition to anxiety in a sample of PD patients with and without depression. A gas mixture of 35% CO₂ and 65% O₂, known to provoke panic in PD patients, was administered to 25 PD patients. Nine of these had a comorbid (current or lifetime) depression and 16 patients did not meet criteria for depression. At baseline, and immediately after the challenge, subjects were assessed on a list of panic symptoms, an adapted Profile of Mood States regarding aggressive and depressive feelings, and visual analogue scales of aggression and depression. All patients reported an increase in anxiety symptoms. PD patients with comorbid depression showed a significantly higher increase on both aggression and depression than did nondepressed PD patients. These findings suggest that a comorbid depression in PD is related to both anxiety and other affective symptoms in response to a CO₂ challenge. Besides its known panicogenic effects, this CO₂ challenge also demonstrates depressogenic and aggressogenic effects, dependent on the comorbid disorder present.

Section IV goes beyond the empirics and attempts to reflect on the interface between anxiety and depression from a different perspective. *Chapter 9* provides a conceptual approach to the relationship between anxiety and depressive

disorders, without questioning the validity of nosological diagnoses. It starts with an overview of current assessment procedures and instruments for anxiety and depression, and reviews the prevalence of comorbidity between anxiety disorders and depressive disorders. The remainder of this final chapter reflects on the concepts of anxiety and depression themselves, and the logical relationships that may follow from their meaning. Our conceptual inquiry into the nature of emotions, focused on fear and sadness as supposed *normal* counterparts of *pathological* anxiety and depression. This followed the conceptualization of Spinoza, as described in 1677 in his book “Ethics”. We provide a perspective in which it is assumed that anxiety and depression are features on a continuous affective spectrum, with no clear overlap. Another framework shortly hinted at in this chapter is the field of evolutionary affective neuroscience, where emotions are conceived of as adaptive functions that have emerged from brain processes because emotions maximized chances for survival.

In the introduction of this thesis, reference was made to multiple meanings of the term ‘interface’. Among its meanings were a boundary between two things, but also an overlap, and interaction between two things. An example of the ‘boundary’ interpretation was seen in the study on suicidal ideation in panic disorder patients. It was shown that *pure* panic disorder patients without comorbid disorders did not report making suicide plans more frequently, nor did they report more suicide attempts than controls. It is known that depression predisposes to suicide. Supposedly, only after ‘crossing the boundary’ with depression, PD patients would also have a higher risk for suicide. But without comorbid depression, there is no increased risk for suicide in PD patients. An example of the ‘overlap’ interpretation could be inferred from the study on sleep complaints in PD patients. It was shown that the complaints of sleep disturbances in PD patients could not only be attributed to nocturnal panic attacks or a comorbid depression. Sleep complaints can be supposed to be a symptom that overlaps PD and depression. The meaning of interface, being ‘interaction’, seems appropriate to reflect the results of the other studies discussed here. For example, the chapters on depression in PD and OCD, both showed an impact of comorbid depressive disorder on symptom severity, and treatment outcome for the index anxiety disorder. This meaning of interface, however, does not rule out a ‘boundary’ or ‘overlap’ interpretation, since two separate disorders might just as well influence one another. Also, overlapping disorders may interact in several ways, e.g. on treatment outcome.

In conclusion, anxiety and depressive disorders share a number of clinical features, they may even belong to the same spectrum. Assessing comorbidity is

important, in disentangling core features from confounders, and in predicting therapeutic outcome. *Studies at the Interface between Anxiety and Depression* has demonstrated that in order to evaluate comorbidity it is essential to empirically assess both 'boundary' and 'overlapping' phenomena of symptoms of anxiety and depression.

SAMENVATTING EN CONCLUSIE

Het veelvuldig gelijktijdig voorkomen van angst en depressie in de klinische praktijk vormde de aanleiding voor dit proefschrift. Verschillende studies werden uitgevoerd in het grensgebied tussen angststoornissen en depressieve stoornissen, en rond aanverwante onderwerpen als suicidaliteit en slaapklachten.

Na een *voorwoord 1* in de *Inleidende Sectie* geeft *hoofdstuk 2* een overzicht van bevolkingsstudies met betrekking tot prevalentie, demografische kenmerken, risicofactoren, natuurlijk beloop en comorbiditeit van de DSM-IV angststoornissen. De geschatte lifetime prevalentie van alle angststoornissen is 25%, vergeleken met ongeveer 17% voor depressieve stoornissen in de populatie. Van alle angststoornissen komen de sociale fobie en de specifieke fobie het meest voor (11-12%). De prevalenties van de andere angststoornissen zijn: paniekstoornis met of zonder agorafobie 2%, obsessief-compulsieve stoornis (dwangstoornis) 2-3%, gegeneraliseerde angststoornis 5%, en ongeveer 7% van de populatie zou een posttraumatische stress stoornis kunnen ontwikkelen. Vanwege diverse factoren zoals selectiebias, ernst van de symptomen, gebruikte diagnostische criteria, en gebruikte meetinstrumenten in de verschillende studies is terughoudendheid geboden bij interpretatie van deze epidemiologische data.

Sectie I begint de beschrijving van de empirische studies met gegevens over comorbiditeit en behandelaspecten van comorbide depressie en angststoornissen. *Hoofdstuk 3* biedt een literatuuroverzicht van de comorbiditeitsgegevens van paniekstoornis en depressie. Daarnaast wordt een retrospectieve studie bij patiënten met een paniekstoornis beschreven. Hoewel de paniekstoornis niet de meest voorkomende angststoornis is, wordt deze in de klinische praktijk wel veelvuldig gezien, met name vanwege de forse beperkingen in het dagelijks leven waarmee patiënten met deze stoornis te maken krijgen. Het voorkomen van comorbide depressie bij patiënten met een paniekstoornis werd onderzocht, teneinde zicht te krijgen op klinische kenmerken en invloed van de comorbiditeit op de behandeling. Van 160 patiënten met een paniekstoornis bleek 30% eveneens te voldoen aan de criteria voor een gelijktijdige depressieve stoornis of dysthymie. De groep paniekpatiënten met een depressie was significant ouder dan de niet-depressieve groep, en meldden ernstiger angst symptomen. Beide groepen verbeterden in dezelfde mate met een gecombineerde farmacologische en

gedragstherapeutische behandeling, zoals bleek uit een afname op gebruikte psychometrische schalen. Deze uitkomsten zijn consistent met een theoretisch model waarin angststoornissen (in dit geval paniekstoornis) predisponeren tot depressie.

Hoofdstuk 4 handelt over de comorbiditeit van de dwangstoornis met depressie, en de betekenis van een comorbide depressie voor het behandelresultaat van de dwangstoornis. Er werd een retrospectief onderzoek gedaan naar de baseline gegevens van 120 patiënten met dwangstoornis en gegevens van 72 patiënten na behandeling. Ruim een derde (37%) van de dwangstoornis patiënten bleek tevens depressief bij aanmelding. De ernst van de dwangsymptomen verschilde bij aanvang niet tussen depressieve en niet-depressieve patiënten, op de algemene angst maten waren de depressieve patiënten wel ernstiger aangedaan dan de niet-depressieve. Zowel depressieve als niet-depressieve dwangpatiënten reageerden goed op de behandeling, zoals bleek uit de metingen van depressieve-, dwang- en algemene angstklachten. Echter, een comorbide depressie bleek toch een negatief effect te hebben op de behandeling, de verbetering bij deze groep was minder groot dan bij de niet- depressieve patiëntengroep, op de meeste onderzoeksparameters. Bovendien, terwijl beide groepen OCD patiënten bij aanvang een gelijke ernst van de dwang lieten zien, na behandeling bleek het eindresultaat voor de depressieve patiënten minder gunstig dan voor de niet-depressieven. Deze bevindingen benadrukken het belang van het herkennen en diagnostiseren van comorbide aandoeningen bij OCD, vanwege hun invloed op de behandeling.

Sectie II bevat verslagen van gerelateerde fenomenen bij de paniekstoornis. *Hoofdstuk 5* gaat in op suicidaliteit in patiënten met paniekstoornis. In deze studie werd alle DSM-IV as I en as II pathologie zorgvuldig geëxcludeerd, om een goed beeld te kunnen krijgen van de mate waarin ‘pure’ paniekstoornis verantwoordelijk zou zijn voor de in eerdere studies gemelde verhoogde kans op suicide in deze groep. Vijftig pure paniekstoornis patiënten (met of zonder agorafobie) werden vergeleken met 50 gezonde, op leeftijd en geslacht gematchte vrijwilligers. Het bleek dat pure paniekstoornis patiënten vaker dan de gezonde controlegroep gepreoccupeerd waren met de dood in het algemeen, en bovendien vaker een passieve doodswens te kennen gaven. Echter, paniekpatiënten hadden niet vaker dan de controles zelfmoordgedachten, zelfmoordplannen of meer zelfmoordpogingen ondernomen. Wij concludeerden hieruit dat de paniekstoornis alleen geen aanleiding geeft tot een hoger suicide risico. Door het zorgvuldig uitsluiten van comorbide stoornissen, werd aangetoond dat het voorheen gerapporteerde verhoogd suicide risico vermoedelijk te wijten is aan (in de praktijk vaak voorkomende) comorbide stoornissen.

Hoofdstuk 6 bespreekt het verband tussen slaapklachten en paniekstoornis. In dit onderzoek werd nagegaan hoe vaak slaapklachten voorkomen bij patiënten met een paniekstoornis in vergelijking met een gezonde controlegroep. Aan 70 paniekpatiënten en 70 gezonden werd gevraagd naar hun subjectieve slaapbeleving, met behulp van een vragenlijst, de Slaap-Waak Ervaringen Lijst (SWEL), die de slaap-waak beleving over een vol etmaal bestrijkt, in de afgelopen 3 maanden. Zevenenzestig procent van de paniek patiënten tegenover 20% van de gezonden rapporteerden slaapklachten. In de groep paniek patiënten had 77% van de patiënten met comorbide depressie en/of nachtelijke paniekaanvallen slaapklachten, tegenover 53% van de *pure* paniek patiënten. Deze verschillen waren significant. Hieruit werd geconcludeerd dat comorbide depressie en nachtelijke paniekaanvallen slechts gedeeltelijk verantwoordelijk zijn voor de verhoogde prevalentie van slaapklachten bij patiënten met paniekstoornis: ook *pure* paniek patiënten, dus zonder nachtelijke paniek en zonder depressie, hebben vaker en meer last van slaapklachten dan controle personen.

Hoofdstuk 7 is een verslag van een replicatiestudie naar de voorspellende waarde van een hoge 'bloed-letsel-fobie' score op de Fear Questionnaire (FQ) voor behandelresultaat van paniekstoornis. In 1995 werd een opmerkelijke studie gepubliceerd door Slaap et al. Deze onderzoekers meldden dat scores op de FQ bloed-letsel fobie sublijst negatief correleerden met het medicamenteuze behandelingsresultaat van een paniekstoornis. In onze studie werden de gegevens van 61 paniek patiënten geanalyseerd, ten tijde van aanmelding en na 12 weken behandeling met een SSRI. Response was gedefinieerd als een afwezigheid van paniekaanvallen en/of een afname van tenminste 50% op de agorafobische vermijding, gemeten met de FQ agorafobie subschaal. Nonresponse werd gedefinieerd door het persisteren van paniekaanvallen. Twintig (32%) patiënten waren nonresponders. Vijfenvijftig procent van deze nonresponders had een hoge score (boven de cutoff van 20) op de I-Q bloed-letsel subschaal, tegenover 19,5% van de responders ($p=.008$). In navolging van Slaap et al. concludeerden wij dat comorbide bloed-letsel fobische symptomen de behandeling van paniekstoornis negatief beïnvloeden.

Sectie III besluit de serie klinische studies. *Hoofdstuk 8* beschrijft een experimenteel onderzoek dat gebruik maakt van de CO₂ provocatie methode. Tot nu toe hebben studies die gebruik maken van deze methode zich voornamelijk gericht op het meten van angst als uitkomstmaat. Het doel van dit onderzoek was om naast angst ook andere affectieve symptomen te meten, in een groep paniekpatiënten met en zonder comorbide depressie. Een gasmengsel van 35% CO₂ en 65% O₂, waarvan bekend is dat het panieksymptomen kan oproepen in patiënten met een paniekstoornis, werd toegediend aan 25 paniek patiënten. Negen van deze groep paniek patiënten

hadden een comorbide depressie (gelijktijdig of in de voorgeschiedenis), 16 patiënten hadden geen depressie (gehad). Zowel voor, als vlak na de provocatie test, vulden de patiënten een vragenlijst met panieksymptomen in, een lijst met stemmings-items, en visueel-analoge schalen met betrekking tot angst, depressieve en agressieve gevoelens. Alle patiënten meldden verhoogde angstsymptomen na de CO₂ test, paniekpatiënten met een depressie vertoonden een significant hogere stijging op depressieve en agressieve symptomen na de test dan niet-depressieve paniek patiënten. Deze uitkomsten suggereren dat een comorbide depressie in paniekpatiënten gerelateerd is aan zowel angst- als agressieve en depressieve reacties op een CO₂ test. Deze provocatie methode blijkt naast paniek-uitlokkende effecten tevens depressieve en agressieve gevoelens te kunnen uitlokken bij paniek patiënten in afhankelijkheid van de comorbide stoornis.

Sectie IV gaat voorbij de empirie en probeert het grensgebied tussen angst en depressie vanuit een ander perspectief te benaderen. *Hoofdstuk 9* biedt een conceptuele benadering van de relatie tussen angststoornissen en depressie, de validiteit van de nosologie buiten beschouwing latend. Dit hoofdstuk begint met een overzicht van enkele veel gebruikte dimensionale en categoriale meetinstrumenten voor angst en depressie, en geeft een overzicht van de comorbiditeits cijfers van angst en depressie. Vervolgens wordt nader ingegaan op de betekenis van de concepten angst en depressie zelf, en de logische verbanden die daaruit zouden kunnen voortvloeien. Onze conceptuele zoektocht naar de aard van emoties, richt zich op vrees en droefheid, als veronderstelde *normale* tegenhangers van *pathologische* angst en depressie. Wij volgen de conceptualisatie volgens Spinoza, zoals beschreven in zijn “Ethica” uit 1677. Wij schetsen een perspectief waarin wordt aangenomen dat angst en depressie uitingen zijn op een continu affectief spectrum, zonder duidelijke overlap. Een ander kader waaraan zijdelings gerefereerd wordt in dit hoofdstuk is het terrein van de evolutionaire affectieve neurowetenschappen, waarin emoties beschouwd worden als adaptieve functies die zich hebben ontwikkeld uit hersenprocessen en waar gesteld wordt dat emoties uiteindelijk overlevingskansen vergrootten.

In het voorwoord van dit proefschrift werd gerefereerd aan de meervoudige betekenissen van het begrip ‘interface’ zoals gebruikt in de titel. Onder andere, betekende ‘interface’ een ‘grensvlak’, en ook kon een ‘overlap’ of ‘interactie’ worden bedoeld. In dit proefschrift zagen we een voorbeeld van de ‘grensvlak’ betekenis in de studie naar suicidaliteit bij paniek patiënten. Hier werd aangetoond dat *pure* paniek patiënten zonder comorbide stoornissen niet vaker dan gezonde controle personen melding maakten van suicideplannen of suicidepogingen. Het is bekend dat depressie tot suicide kan leiden. Blijkbaar is

het zo dat paniekpatiënten pas na het ‘oversteken van de grens’ met depressie een verhoogd suiciderisico hebben. Maar zonder deze comorbiditeit, is er geen verhoogd suiciderisico.

Een voorbeeld van de ‘overlap’ interpretatie van ‘interface’ werd gezien in de studie naar slaapklachten bij patiënten met een paniekstoornis. Dit onderzoek wees uit dat comorbide depressie en nachtelijke paniekaanvallen bijdragen tot het voorkomen van slaapklachten, maar onvoldoende zijn om alle slaapklachten bij paniek patiënten te verklaren. Slaapklachten kunnen beschouwd worden als een overlappend symptoom bij zowel paniek als depressie. De laatste betekenis van ‘interface’, zijnde ‘interactie’, is toepasbaar op de overige beschreven studies. Bijvoorbeeld, de hoofdstukken over comorbide depressie in paniekstoornis en OCD lieten zien dat de aanwezigheid van de depressie een duidelijke invloed had op de ernst van de angstsymptomen, en op het behandelingsresultaat van de betreffende angststoornis. Maar dit wil niet zeggen dat deze laatste betekenis van ‘interface’ de beide anderen uit sluit. Twee onafhankelijke stoornissen kunnen immers evengoed interactie geven, en zo kunnen ook twee elkaar overlappende aandoeningen op verschillende manieren wederzijdse invloed uitoefenen.

Concluderend, angststoornissen en depressieve stoornissen hebben een aantal klinische kenmerken gemeenschappelijk. Ze zouden zelfs tot een zelfde spectrum kunnen behoren. Het beoordelen en diagnosticeren van comorbiditeit is van wezenlijk belang om kernsymptomen van ruis te onderscheiden, en om goede voorspellingen mogelijk te maken van behandel effecten. *Studies at the interface between anxiety and depression* heeft aangetoond dat het essentieel is om zowel de grensgebieden als de overlappende terreinen empirisch te toetsen, teneinde zo het gehele spectrum te kunnen beoordelen van angst en depressie.

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CURRICULUM VITAE

Thea Overbeek werd geboren op 11 maart 1959 te Gendringen. Zij volgde het Atheneum-A aan de Protestants-Christelijke Scholengemeenschap te Doetinchem van 1971 tot 1977. Van 1977 tot 1981 studeerde zij Psychologie aan de Katholieke Universiteit van Nijmegen en sloot dit af met het kandidaatsexamen. Na een colloquium doctum voor natuur- en scheikunde te hebben behaald werd zij in 1981 toegelaten tot de studie Geneeskunde, eveneens aan de Katholieke Universiteit van Nijmegen en behaalde in 1988 het arts-examen. Hierna heeft zij in verschillende ziekenhuizen (Nieuwegein, Delft, Utrecht) gewerkt als arts-assistent pathologie, tot zij in 1993 overstapte naar de psychiatrie. Zij werkte als arts-assistent psychiatrie in een ambulante setting te Weert en als afdelingsarts in de Bernard Lievegoed Kliniek te Bilthoven. Sinds 1995 is zij werkzaam als afdelingsarts op het Academisch Angst Centrum (AAC) te Maastricht, een geacademiseerde afdeling van het Psycho-Medisch Streekcentrum Vijverdal, tevens Teaching Hospital. Zij combineerde haar klinische werkzaamheden met de wetenschappelijke studies die in dit proefschrift resulteerden.

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