MOOD AND ANXIETY DISORDERS

COMORBIDITY AND IMPLICATIONS FOR TREATMENT WITH ANTIDEPRESSANTS

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MOOD AND ANXIETY DISORDERS

Comorbidity and implications for treatment with antidepressants

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Contents

1 General introduction

The past three decades have witnessed considerable progress in the pharmacological treatment of mood[1] and anxiety disorders. Tricyclic antidepressants (TCA) were initially available for the treatment of major depression, but pharmacological treatment options have been extended with the introduction of selective serotonin reuptake inhibitors (SSRI). The efficacy of antidepressants has also not been restricted to mood disorders. Patients with anxiety disorders also appear to benefit from treatment with antidepressants, and introduction of new antidepressants has enhanced the treatment possibilities. Even though there is growing knowledge of the efficacy of different antidepressants and their range of utility, it is still not possible to predict antidepressant treatment response in mood and anxiety disorders or to meaningfully differentiate between TCAs and SSRIs. The prescription of antidepressants in primary care facilities and in psychiatric services is therefore not based on consensus. To illustrate, the Dutch depression guideline for general practitioners (Van Marwijk et al., 1994) and the American guidelines for the treatment of depression are not the same because they are based on different empirical evidence (Persons, Thase, & Crits-Christoph, 1996). Further study to detect any differences in the efficacy of different treatments with antidepressants is thus needed. As soon as more is known about the differential efficacy of various antidepressants, treatment indication can be enhanced, and thereby more efficient treatment fostered as well. Further study may also help us understand the underlying mechanisms better as well. Mood and anxiety disorders are the most prevalent psychiatric disorders (Lepine, Wittchen, & Essau, 1993; Bijl, Van Zessen, & Ravelli, 1997) with a high risk of recurrence for mood disorders (Angst, 1996), which makes the ongoing search for the most effective treatments particularly important.

Many questions remain unanswered. When should we prescribe antidepressant treatment? What antidepressant should we prescribe to a patient with major depression or a panic disorder or to a patient with a major depression and co-occurring panic attacks? Why do antidepressants work for a wide range of mood and anxiety disorders? Do antidepressants work differently for mood and anxiety disorders as separate disorders or are disturbed mood and anxiety different aspects of the same underlying disorder?

In the present study, an attempt will be made to answer a number of these questions.

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[1] For purposes of the present study, mood disorders are restricted to major depressive disorders and dysthymic disorders. Bipolar disorders are beyond the scope of the present study.

1.1 Comorbidity of mood and anxiety disorders

With the development of standardised classification systems such as the Diagnostic and Statistical Manual of Mental disorders (DSM) (APA, 1980, 1987, 1994), consensus on psychiatric diagnoses has improved. The current version of the DSM, the DSM-IV, is widely accepted and enables clinicians as well as researchers to use the same categorical language. The DSM is highly descriptive and categorises mood and anxiety disorders as separate disorders. While the DSM criteria sets for the disorders differ, the diagnostic overlap between mood and anxiety disorders is quite high and comorbidity often appears to be the case. In the present thesis *comorbidity* means that *more than one psychiatric disorder can be diagnosed in the same person* (Maser & Cloninger, 1990) (also see Chapter 2).

The existence of comorbidity between mood and anxiety disorders is an important, although often ignored, issue in interpreting treatment outcome. The efficacy of antidepressants is usually studied in patient populations selected on the basis of the DSM criteria. Comorbidity is also frequently used as an exclusion criterion even though comorbid symptoms of mood and anxiety disorders are the rule rather than the exception in clinical practice (Wittchen, Essau, & Krieg, 1991). This situation greatly limits the generalisation of research findings to clinical practice. More important is the assumption that the selection of 'homogeneous' or 'pure' patient groups can help us find specific treatment indications. To illustrate, with the exclusion of major depression, researchers assume that they are studying a diagnostically 'pure' group of anxiety disorder patients. In fact, however, only those patients with a clear clinical picture, such as severe depression, are recognised and excluded. Patients with other types of depression are most likely included, which means that comorbidity is present. The use of DSM criteria to select patient groups thus suggests that a different population is included in a study on major depression than in a study on anxiety disorders. DSM categorisations imply the existence of different syndromes. In practice, however, partly the same patients may be treated for major depression in one study and anxiety disorder in the other. To illustrate this point, in a meta-analysis of clinical trials concerned with generalized anxiety disorder or major depression, one-third of the generalized anxiety disorder patients were found to have depressive symptoms severe enough to be entered into the major depression trials. Two-thirds of the major depression patients were found to have anxiety symptoms severe enough to enter the trials on generalized anxiety disorder (Copp, Schwiderski, & Robinson, 1990).

In conclusion, appropriate classification of mood and anxiety disorders remains difficult due to widespread comorbidity. The DSM criteria do not adequately distinguish these patient groups. In fact, the existing overlap in mood and anxiety symptoms raises the question of whether mood and

anxiety disorders are actually different disorders or part of the same syndrome. Furthermore, when different antidepressants (e.g., TCA versus SSRI) are studied with these presumably 'pure' groups, the question remains as to whether the treatments really have the same effect when they do not produce significantly different results. It is unknown if the patient recovered from mood symptoms, a co-existing anxiety disorder or vice versa. In other words possible differences between antidepressants can remain undetected when patient selection is based on the DSM criteria.

1.2 Antidepressant treatment response in mood and anxiety disorders

There is a general consensus that a positive response to treatment with antidepressants is not limited to mood disorders. Initially, tricyclic antidepressants (e.g., imipramine, clomipramine) were indicated for depressed patients (Morris & Beck, 1974). Treatment response was best predicted in patients with melancholic symptoms (Bielski & Friedel, 1976). Tricyclic antidepressants also turned out to be effective for the treatment of anxiety disorders as well and particularly for patients with panic disorder or obsessive compulsive disorder (McTavish & Benfield, 1990; Van Balkom, 1994). Interestingly, the efficacy of the treatment could not be explained in terms of antidepressant response because patients without comorbid depressive symptoms responded as well. The antidepressant treatment options expanded with the development of selective serotonin reuptake inhibitors (SSRI), which are registered as antidepressants. As with the TCAs, the SSRIs also proved effective for the treatment of anxiety disorders, initially studied primarily in patients with panic disorder and obsessive compulsive disorder (Boyer, 1995; Den Boer & Westenberg, 1988; Jefferson, 1997; Piccinelli, Pini, Bellantuono, & Wilkinson, 1995; Stein, Spadacinni, & Hollander, 1995; Van Balkom, 1994). In placebo controlled studies, SSRIs have also been found to be effective for the treatment of social phobia (Allgulander, 1999; Baldwin, Bobes, Stein, Scharwächter, & Faure, 1999; Stein, Fyer, Davidson, Pollack, & Wiita, 1999; Stein et al., 1998). Venlafaxine, another modern antidepressant, has been registered recently for the treatment of generalized anxiety disorder. Overall, no significant differences have been found between response to SSRIs and TCAs for the treatment of anxiety disorders.

In clinical practice, antidepressant treatment has become a valuable option for a large group of patients. Nevertheless, the current empirical evidence regarding the differential effects of TCAs and SSRIs is limited. The only difference that can be stated is that TCAs are probably more effective for the treatment of severe major depression than SSRIs (Kraghsorensen, 1990; Elkin et al., 1995; Anderson & Tomenson, 1994; Anderson, 1998). At least, the opposite has never been found. A possible explanation for the

better response of patients with severe major depression to TCAs is that severe cases are generally easy to classify. The symptoms are sufficiently severe to be recognised as part of a depressive disorder and, as a consequence, a relatively 'pure' patient group is studied. This is also, then, in line with the classical findings of Bielski and Friedel (1976) who found melancholic symptoms to best predict TCA response. The symptoms were loss of appetite, loss of weight, early morning awakening and retardation versus agitation. A subgroup of patients can thus be identified as responding favourably to TCAs on the basis of the severity and specificity of their symptoms. Diagnostic expressions such as 'depressive neurosis' or 'endogenous' 'vital' or 'melancholic' depression have been used to identify such subgroups, although their etiological background remains unknown. Interestingly, two psychobiological indicators, clinical severity and an abnormal EEG sleep profile, have been associated with poorer response to cognitive behaviour therapy (Thase, Simons, & Renold, 1996). These findings again suggest the existence of a subgroup of severely depressed patients with a differential treatment response. Although a pharmacotreatment group was not included in the latter study, it may be hypothesised that these patients would respond favourably to TCAs. This is also consistent with earlier research in which patients with a major depression and a shortened rapid eye movement latency were found to respond favourably to TCAs (Rush et al., 1985).

A caveat in the empirical evidence showing more severely depressed patients to respond better to TCAs than SSRIs is a possible selection bias. More specifically, part of the severe patient population may have been non-responders to initial treatment with an SSRI because that is the treatment of first choice. In current guidelines for the treatment of depression, it is recommended that one starts with an SSRI, due to better tolerability and fewer side effects (Schulberg, Katon, Simon, & Rush, 1998). In other words, the treatment history of severely depressed patients may bias outcome results (Bouvy, 1997). Such a selection bias may be particularly the case in more recent studies as a result of the growing acceptance of SSRIs over the past decennium. Furthermore, few inpatient studies have compared TCAs to SSRIs (Boyer, 1995).

Apart from the evidence that TCAs are probably more effective for the treatment of severely depressed patients, no differences in the efficacy of TCAs versus SSRIs have been found (Anderson & Tomenson, 1994). Patients with milder symptoms of depression or patients with an anxiety disorder showed no differences in response. One explanation is that differential diagnosis is more difficult in less severe cases as already mentioned. Patients with mood or anxiety disorders show a large degree of overlap in their symptoms. Correlations between severity measures for anxiety and depression are also found to be consistently high, about .70 (Bouman, 1987). As pointed out earlier, the DSM criteria have proved inadequate to distinguish these patient

groups although the criteria are generally used for patient selection. Inconsistent categorisations may occur and possible differences between TCA and SSRI response go undetected due to the overlap in the symptoms of the different groups. In anxiety disorders, no differential response is detected (Van Balkom, 1994) but this does not mean that TCAs and SSRIs are equally effective in practice. The effect sizes varied per treatment condition for obsessive compulsive disorder patients[2]. For the treatment of an obsessive compulsive disorder the efficacy of clomipramine (a partial selective serotonin re-uptake inhibitor) is generally accepted in clinical practice although differential effects of SSRIs and TCAs have not been consistently found. Due to the very few placebo-controlled studies with a large number of subjects and the lack of studies with TCAs, meta-analyses are also not able to demonstrate a differential response (Stein et al., 1995; Van Balkom, 1994). TCAs are studied more frequently in connection with panic disorder. Nevertheless, in only one meta-analysis (Boyer, 1995) SSRIs were found to be significantly superior to imipramine. It should be noted, however, that with a sufficiently high dosage of imipramine, the SSRIs were no longer superior. Overall, no differential response for TCAs versus SSRIs is found.

In conclusion, although the DSM is widely accepted, classification according to the DSM has not resulted in the identification of the proper patient groups for treatment with specific antidepressants. The question which remains is whether the DSM has been consistently followed in clinical practice. Structured interviews are mainly used for research purposes, but most studies do not report use of a systematic procedure to acquire the DSM diagnosis. The role of selection bias is also often ignored in treatment outcome studies although it has important consequences for the interpretation of the research results.

How to detect differences in antidepressant treatment response?

The high comorbidity between mood and anxiety disorders, diagnosed with the DSM, raises problems in interpretation of current clinical research. As part of this, research has not been able to find differences in antidepressant treatment response. Alternative models may help to identify patient groups that are supposed to be of relevance to detect antidepressant treatment differences.

[2] Meta-analysis of the efficacy of antidepressants in obsessive compulsive disorder: n=number of studies: clomipramine n=21, Cohen=s *d*=1.71, SD=1.01; fluvoxamine n=7, Cohen=s *d*=1.38, SD=0.72; imipramine n=2, Cohen=s *d*=1.55, SD=0.32 (Van Balkom, 1994)

1.3 The role of primary diagnosis

One approach to the phenomenon of comorbidity has been the use of the primary-secondary diagnosis distinction. Initially the distinction of primary and secondary diagnosis was restricted to chronology. The disorder that came first chronologically is viewed as the primary diagnosis. Once again, the primary-secondary distinction is used to generate homogeneous groups and thereby contribute to our knowledge of aetiology (Klerman, 1990). Although the term primary diagnosis is often used in other senses (e.g., to indicate the predominance of a particular clinical feature), the chronology perspective may be most suited to the detection of the types of depression related to treatment differences. In the present thesis, the term *primary diagnosis* refers to *the diagnosis that comes first chronologically* or, in other words, the diagnosis at first episode.

Cloninger and colleagues (1990) adopted this chronology perspective to distinguish depressed patients according to their comorbid diagnosis and stated the importance of determining the first disorder of a person for etiological reasons and treatment choices. Primary depression has been distinguished from secondary depression or 'demoralisation depression'. The hypothesis is that secondary depression is usually a nonspecific demoralisation reaction. The risk of a depressive disorder in chronic anxiety patients is also higher than the risk of an anxiety disorder in patients with depressive disorders. Finally, it is very rare for an anxiety disorder to be a chronic residual state following remission of a primary depressive disorder (Cloninger, Martin, Guze, & Clayton, 1990).

Winokur (1997) has also emphasised the importance of the chronology of disorders to detect different types of depression despite no differences in current symptomatology. In doing this, he distinguished 'familial pure depressive disease (FPDD)' from 'depression spectrum disease (DSD)' as DSD is seen in emotionally unstable individuals, characterised by pre-existing psychiatric or personality disorders and/or associated with a family history of alcoholism. Secondary depression is considered equal to DSD. Research findings show that FPDD patients respond better to pharmacotreatment and electroconvulsive treatment than DSD patients. Winokur has also therefore argued for the importance of distinguishing subtypes of depression based on other levels of pathology than current symptomatology. That is, other classification dimensions, such as chronology of the disorders, may be relevant for the detection of etiological subtypes although the current clinical picture may not differ. Finally, Winokur has emphasised the need for etiological homogeneous patient groups to predict pharmacotreatment response more adequately.

1.4 The role of temperament

The psychobiological personality model of Cloninger (Cloninger, 1987; Cloninger, Svrakic, & Przybeck, 1993) is yet another model with implications for treatment response. The model has been reputed to differentiate between responders and nonresponders to antidepressant treatment (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). The model consists of four basic dimensions of temperament: Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence. The different dimensions refer to automatic emotional responses which are moderately heritable and stable throughout life. Large-scale twin studies have confirmed that the temperament dimensions are genetically homogeneous and independent of one another (Heath, Cloninger, & Martin, 1994; Stallings, Hewitt, Cloninger, Heath, & Eaves, 1994). According to the theoretical model, the temperament dimensions may also be related to an increased susceptibility to different neurotic syndromes (Cloninger et al., 1993). Harm Avoidance is postulated to relate to the functions of the serotonergic brain system or, in other words, the behavioural inhibition system. Harm avoidance is thought to reflect a heritable tendency to intensely respond to aversive stimuli and thereby a tendency to inhibit behaviour to avoid novelty, the frustration of nonreward and punishment. A passive avoidance pattern thus appears. In line with this, Harm Avoidance scores have been found to be elevated in anxiety disorder patients and mood disorder patients. Harm Avoidance is assumed to be directly related to a susceptibility to anxiety disorders. In contrast, different subtypes of depression have been related to interactions between temperaments. For example, high Harm Avoidance in combination with high Novelty Seeking is assumed to lead to dysthymia due to continuing approach-avoidance conflicts within the individual. Furthermore, high Reward Dependence is assumed to be related to a heightened sensitivity to loss, which then in turn produces the reactive dysphoria characteristic of atypical depression. Cloninger concluded on the basis of the existing empirical evidence that depressives are clinically and etiologically heterogeneous and that temperament is a more powerful means of characterising this heterogeneity than depressive symptomatology or comorbid psychopathology (Cloninger et al., 1994). The study of personality temperaments also presents a useful perspective for the present study. Rather than focus on single DSM categorisations based on current symptomatology, the personality model enables an alternative typology of patients based on temperament. Classification of patients according to temperament may then provide insight into different responses to antidepressant treatment in patients with mood and/or anxiety disorders. The present study is thus an initial exploration of a possible relation between temperament scores and treatment outcome within a broad range of patients with the attempt to identify relevant subtypes.

1.5 Main research questions addressed in this thesis

The aim of the present study was to examine the differential responses to treatment with TCAs versus SSRIs for a broad range of mood and anxiety disorders. Alternative models for the identification of subgroups differentially responding to antidepressant treatment were explored. The use of systematic diagnostic procedures for the selection of the patient sample was also of particular interest. The present study thus has two main areas of interest: 1) diagnostic accuracy for mood and anxiety disorders and 2) antidepressant treatment response.

1. *How accurately do we diagnose mood and anxiety disorders? More specifically, what is the agreement between clinical diagnosis and diagnosis based on a structured diagnostic instrument? (Chapter 5)*

2. *Are we able to differentiate TCA and SSRI response in patients with mood and anxiety disorders using alternative classification models? More specifically,*
   a) *is it possible to differentiate antidepressant treatment response in patients with mood and anxiety disorders based on their primary diagnosis (e.g., diagnosis at first episode)? (Chapter 6)*
   b) *does temperament, according to the personality model of Cloninger, appear to be related to a differential antidepressant treatment response in patients with mood and anxiety disorders? (Chapter 7)*

1.6 Outline of the contents

In the *second chapter* issues regarding the comorbidity of mood and anxiety disorders will be considered in greater detail along with the implications for research. In the *third chapter,* the psychobiological personality model of Cloninger and the corresponding inventory, the Tridimensional Personality Questionnaire (TPQ), will be presented. In the next chapters, the results of the empirical research will be presented. First of all, in the *fourth chapter*, an outline of the research project will be given. Special attention is paid to the patient selection procedures and the sample sizes analysed to answer the different research questions. In the *fifth chapter*, the degree of agreement on the diagnoses of mood and anxiety disorders will be examined. Clinical diagnosis and diagnosis based on a structured diagnostic interview will be compared in particular. In the *sixth chapter,* the role of primary diagnosis or the diagnosis at first episode in a patient's lifetime will be explored in an attempt to detect differences in the responses of patients to antidepressants. Two antidepressants, imipramine (a TCA) and fluvoxamine (an SSRI), will be

examined in a 6-week study of patients with mood or anxiety disorders. In the *seventh chapter,* the results regarding the relation between temperament and response to antidepressant treatment will be presented. Finally, in the *eighth chapter*, the general results and implications of these will be outlined. In addition, some limitations on the present study and suggestions for further research will be provided.

2 Comorbidity of mood and anxiety disorders

Together with the growing acceptance and use of such diagnostic classification systems for psychopathology, as the DSM[3] and ICD[4], the comorbidity of different disorders has become increasingly apparent. The comorbidity of mood and anxiety disorders has been shown to be particularly common. In line with the Kraepelinian disease model, the DSM makes a clear distinction between mood and anxiety disorders using specific criteria sets and exclusion/inclusion rules. This suggests discrete and independent disease entities and as a consequence, both clinicians and researchers often assume clear diagnostic categories. Nevertheless, the existence of comorbidity tells us that mood and anxiety disorders are not always easy to distinguish. Patients with milder depressions and/or more pervasive anxiety are particularly difficult to distinguish and classify. Comorbidity also raises problems with regard to the inclusion of specific patient groups for research purposes (e.g., patients with a panic disorder). Nevertheless, most outcome research is concentrated on a single diagnostic category with the intention to study a 'pure' patient group. Selection bias may appear in the form that only the most extreme or clear-cut cases will be recognised and excluded in line with the exclusion rules, which can clearly influence research findings and treatment choices. Furthermore, the prevalence of comorbidity raises questions regarding the disease entity underlying mood and anxiety. Are mood and anxiety disorders actually different diseases or is there one underlying disease? This is of obvious interest for research on the efficacy of antidepressant treatment. In the search to detect and understand any differences in antidepressant treatment response, an alternative approach is to include patients within a broad spectrum of mood and anxiety disorders in order to cope with comorbidity and decrease selection bias.

In the present chapter issues of comorbidity will be discussed in greater detail. A definition and different types of comorbidity will be presented, drawing on the somatic view of comorbidity (2.1). Thereafter, a number of models of comorbidity will be presented (2.2). Furthermore, an overview of the empirical evidence on the comorbidity of mood and anxiety disorders will be

[3] The Diagnostic and Statistical Manual of Mental Disorders has been revised from DSM-III (American Psychiatric Association, 1980) to DSM-III-R (APA, 1987) to DSM-IV (APA, 1994), which is currently in use.

[4] The International Classification of Diseases, published by the World Health Organization, has been revised from the ICD-9th edition revised (WHO, 1977) to the ICD-10 (WHO, 1990).

presented, with a focus on the critical issues in comorbidity research (2.3), prevalence (2.4), the overlap of symptoms (2.5), sequential relationship (2.6) and clinical implications (2.7).

2.1 Somatic view of comorbidity

2.1.1 Definition of comorbidity

Although frequently used in research and practice, the term comorbidity remains poorly defined and lacks clear conceptualisation (Maser & Cloninger, 1990). The term *comorbidity*, introduced by Feinstein (1970), refers to "any additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (pp. 456-457). Feinstein based his description of comorbidity on somatic medicine and restricted the term to diseases or disorders and not symptoms. This concept of comorbidity is also used in the field of psychopathology to indicate that more than one psychiatric disorder can be diagnosed in one and the same person (Maser & Cloninger, 1990).

Feinstein's view of comorbidity pertains to treatment outcome for specific disease entities and follow-up study, and thus implies a longitudinal perspective on comorbidity. However, in many clinical studies, the term comorbidity is also used to describe symptomatic overlap irrespective of whether the phenomena meet the criteria for a mental disorder, although strictly speaking, comorbidity refers to diseases or disorders (Latin: morbus = illness) (Wittchen, 1996).

Compared to Feinstein's somatic view of comorbidity, the more recent definitions of comorbidity in the field of psychopathology have not improved much. To illustrate, Boyd et al. (1984) defined comorbidity primarily for epidemiological studies as 'the relative risk for a person with one disorder to acquire another disorder'. Burke, Wittchen, Regier and Sartorius (1990) defined comorbidity as 'the presence of more than one specific disorder in a person in a defined period of time'. Beyond the inclusion of a time frame, there are no essential changes in the definition compared to the earlier definition of Feinstein. Not one of the definitions, moreover, is uniformly accepted. In the present dissertation, *comorbidity* is viewed in line with Maser and Cloninger (1990), namely *that more than one psychiatric disorder can be diagnosed in the same person*. Psychiatric disorders must be viewed as 'clinical entities' as opposed to diseases as long as the pathogenic mechanisms underlying psychiatric conditions remain unknown. The operationalisation of psychiatric conditions is largely a matter of consensus based on current knowledge as represented in the DSM and the ICD, and the study of psychiatric comorbidity thus relies heavily on the acceptance of current diagnostic classification systems.

2.1.2 Types of comorbidity

Thirty years ago, Feinstein (1970) described the importance of studying comorbidity and this description is largely in line with the basic assumptions of this thesis. Feinstein stated that the neglect of comorbidity has many detrimental effects on general disease statistics and that the worst clinical consequences occur during efforts to evaluate treatment. To evaluate different modes of therapy, clinicians usually assemble two or more groups of patients and compare their treatment responses. For scientifically valid comparison, the groups must be initially comparable. In addition, only randomised trials are considered acceptable for drawing conclusions. Without this pretherapeutic similarity and randomised treatment, the different therapies cannot be properly evaluated.

The usual method of identifying the comparability of patient groups is to note similar *diagnoses, demography* and *anatomy.* In other words, all the patients usually have the same disease; they may also be similar in age, race and sex; and cancer patients, for example, may all have the same anatomic stage of dissemination. Although patients are similar with regard to the afore mentioned categories, they may nevertheless show major differences with regard to *clinical* features. Among the clinical features listed by Feinstein are the mode of detection of the disease, the cluster of symptoms and signs, and the sequence and timing of the symptoms. Even when these clinical features are added to the classification, groups of 'similar' patients may still largely differ with regard to comorbid diseases which can affect the outcome of therapy. If comorbidity is ignored, observed differences in treatment outcome for a particular disease may be attributed to the treatment and not to undetected associated diseases in the patient. The opposite is also possible; that is, no differences in the treatments for a particular disease do not automatically imply equally effective treatments because comorbidity may mask possible differences.

Although Feinstein illustrated the importance of classifying comorbidity for the evaluation of cancer treatments, recognition of comorbidity is also important in research comparing treatment outcome for mood and anxiety disorders. Different responses to different antidepressant treatments for mood and anxiety disorders may go undetected as a result of comorbidity. The comorbid disorder (mood or anxiety) may simulate the index disease (anxiety or mood), with no identification of the initial disorder as a result. Furthermore, patients diagnosed with an anxiety disorder in one study may be diagnosed with a mood disorder in another study. It is here, thus, that the problems associated with the evaluation of antidepressant treatment outcome for mood and anxiety disorders arise as a result of comorbidity is omitted.

Based on previous work, Kaplan and Feinstein (1974) introduced three types of comorbidity which arise in medicine and may be of interest in psychiatry as well. The focus of their research was on the importance of classi-

fying initial comorbidity for evaluating the outcome of treatment for diabetes mellitus. In order to do this, they distinguished pathogenic, diagnostic and prognostic comorbidity.

Pathogenic comorbidity arises when a particular disease leads to certain other complications or diseases, which are therefore considered etiologically related. Kaplan and Feinstein give the example of various cardiovascular-renal system diseases (e.g., hypertension, cardiac disorders excluding cor pulmonale, peripheral vascular disease, retinopathy and cerebrovascular disease), which are commonly regarded as pathogenically related to diabetes. In psychiatry, an example is the development of agoraphobia secondary to recurrent panic attacks, or major depression secondary to a psychiatric disorder of a chronic nature such as schizophrenia. In the present dissertation, primary and secondary depression are distinguished based on chronology. This is in line with the pathogenic comorbidity concept. Secondary depression following a chronic anxiety disorder thus constitutes pathogenic comorbidity.

Diagnostically comorbid diseases share common symptoms. Diagnostic comorbidity is likely whenever the diagnostic criteria are based on patterns of symptoms which are not individually specific. Kaplan and Einstein give polyuria as an example of a symptom found in a patient who has both diabetes mellitus and a coexisting renal ailment which can produce polyuria. The coexisting renal ailment is diagnostically comorbid. In the field of psychiatry, diagnostic comorbidity is common in the sense that the current DSM classification of psychopathology includes nonspecific criteria which may also stem from other disorders. Examples are diminished ability to concentrate because of both a mood and a generalized anxiety disorder or loss of weight due to both a mood and an eating disorder. Excessive worry may be a symptom of generalized anxiety disorder, a mood disorder or an obsessive compulsive disorder and social phobia may be an associated feature of a major depressive disorder (APA, 1994).

Another illustration of diagnostic comorbidity arises in the classification of personality disorders. The differential diagnosis of axis I and axis II personality disorders is complicated by shared features. The diagnosis of borderline personality disorder lacks specificity and shows diagnostic comorbidity with mood disorders. Furthermore, comorbidity of axis II disorders is common. In fact, more patients are diagnosed with two or more personality disorders than with one. The ten personality disorders can be grouped into three clusters based on descriptive similarities: Cluster A (odd cluster) includes paranoid, schizoid and schizotypal personality disorders; Cluster B (dramatic cluster) includes the antisocial, borderline, histrionic and narcissistic personality disorders; Cluster C (anxious cluster) includes the avoidant, dependent and obsessive compulsive personality disorders. Comorbidity occurs not only within clusters (e.g., coexistence of borderline and

histrionic personality disorders both included in the odd cluster) but also between clusters (e.g., coexistence of the borderline and dependent personality disorders from the odd cluster and the anxious cluster, respectively).

Prognostic comorbidity is spoken of when disorders predispose a person to develop other disorders. Kaplan and Feinstein give the example of a patient with diabetes and hypertension being more likely to develop retinopathy than a patient with diabetes alone. A comparable example from the field of psychiatry is the increased risk of alcoholism in a patient with both a panic and a mood disorder. That is, the combination of the two disorders is more likely to precipitate alcoholism than either one alone (Maser & Cloninger, 1990). Yet another example from current research is the increased risk of children with attention-deficit/hyperactivity disorder to develop an antisocial personality disorder later in life (Barkley, 1998).

Although Kaplan and Feinstein based their types of comorbidity on somatic medicine, the types are useful for understanding comorbidity in psychopathology as well. The present thesis is based on the assumption that the comorbidity between mood and anxiety disorders is often neglected in outcome research, and that such neglect may clearly influence treatment results. More specifically, possible differences between antidepressant treatments may go undetected due to a neglect of comorbidity. The groups of patients being compared may not be as similar as proposed. Diagnostic comorbidity of mood and anxiety disorders appears to be the case for DSM classification, even though the DSM requires separate diagnoses. Of particular interest in the present thesis, however, is the search for pathogenic and prognostic comorbidity, because this can help unravel the pathogenesis of mood and anxiety disorders. The objective of the present study is thus to include all patients with a mood and/or an anxiety disorder and differentiate them according to primary diagnosis or the diagnosis which occurs first in life. In doing this, the selection bias which usually occurs in studying single diagnostic categories will be reduced. In addition to patients with a clear clinical picture of major depression or an anxiety disorder, comorbid cases which are usually difficult to classify will also enter the study. No artificial choices are made during the classification procedure and the primary diagnosis will play a critical role in the measurement of treatment outcome which is in line with the concept of pathogenic comorbidity. For this reason, the current DSM categories are also not studied in the present study. Diagnostic comorbidity problems would arise and possible differences in the efficacy of antidepressants for subgroups of patients would go undetected. The search for pathogenic comorbidity in terms of primary versus secondary depression and primary anxiety is thus assumed to be a more valuable focus for the evaluation of antidepressant treatment response.

2.2 Models of comorbidity

Another way of approaching comorbidity is to examine different models of comorbidity. Three conceptual models of the relationship between mood and anxiety have been distinguished by Stavrakaki and Vargo (1986); the unitary model, the pluralistic model and the mixed anxiety-depression model. Although the concept of pathogenic comorbidity appears to be best suited to the purposes of the present research, the different models distinguished will also be considered below.

The *unitary model* presents mood and anxiety symptoms as variants of the same affective disorder. Mood and anxiety disorders are represented along a continuum and thus differ only quantitatively. The overlap in the clinical symptomatology associated with mood and anxiety disorders has been cited as the greatest source of support for this model. Further support for the unitary model comes from treatment studies in which anxiety disorder patients have been found to respond favourably to antidepressants. The tendency for patients with long standing anxiety disorders to develop mood symptoms is also cited as support for the unitary model (Stavrakaki & Vargo, 1986).

The *pluralistic model* presents mood and anxiety as separate and qualitative distinct entities. Although the overlap in symptomatology is recognised, it is argued that the use of appropriate measures and statistics will show the two disorders to clearly differ along certain dimensions. The relevant research data concerns differences in clinical characteristics, rating scales, prognosis, personality, treatment response, course and outcome, physiological response to stress and family history data (Stavrakaki & Vargo, 1986). Despite these efforts, however, it has not been possible to detect important differences between patients with mood versus anxiety disorders.

The *mixed anxiety-depression model* consists of three groups. In addition to patients with discrete mood disorders and patients with discrete anxiety disorders, a mixed group of patients is distinguished. Research indicates that when the two disorders coexist, there is increased chronicity, reduced treatment response and a poorer prognosis. Mood and anxiety in combination are thus argued to represent a quantitative and qualitative distinct disorder when compared to either mood disorder or anxiety disorder alone.

Each of the above models has its own heuristic value for the description of the possible relationships between mood and anxiety. It has been proposed that mood and anxiety disorders are no more than two surface manifestations of a 'general distress factor'. Efforts to define separate mood and anxiety disorders are therefore limited by the features common to the different disorders and an artificial splitting of a complex syndrome into separate parts is suggested by the unitary view of comorbidity (Frances et al., 1992).

The unitary model in its purest form combines all mood and anxiety disorders into a single complex syndrome with the same underlying pathogenesis.

Despite a great deal of overlap, relatively 'pure' or distinct disorders have also been observed which raises the need for both a unitary model and a pluralistic model or what, in fact, is a mixed anxiety-depression model. The tripartite model of anxiety and depression (Clark & Watson, 1991) is such a mixed anxiety-depression model. Based on factor-analytic studies, Clark and Watson suggested that anxiety and mood disorders be reorganised into three groups: 1) generalised mood disorder (characterised by general distress, anxiety and low mood); 2) major depressive disorder (characterised by pervasive anhedonia and lack of positive affect) and 3) major anxiety disorder (characterised by somatic symptoms of hyperarousal which best discriminates anxiety from mood disorder). In line with this, generalized anxiety disorder and major depression have been found to be genetically related, and a shared genetic factor has also been found for phobia and panic disorder (Kendler et al., 1995).

2.3 Critical issues in comorbidity research

The co-occurrence of mood and anxiety disorders has been studied extensively over the past 30 years. One of the main findings is that the observed comorbidity rates differ enormously across studies (15% to 91%). Comorbidity rates may differ depending on the population being studied. Epidemiological studies show least one third of all current cases in the general population to meet the criteria for more than one disorder. Comorbidity rates in primary health-care settings indicate an even higher co-occurrence rate with clinical psychiatric inpatient and outpatient studies demonstrating the highest comorbidity rates (Wittchen, 1996). Nevertheless, there is still considerable variation in the comorbidity rates due to different uses of the term across studies. Based on Wittchen (1996), consideration of several critical issues can help us understand the variability in findings regarding psychopathological comorbidity.

Conceptual differences

The term comorbidity is used to indicate an overlap in symptoms as well as descriptive classes of disorders and stresshold conditions. The observed overlap between mood and anxiety can depend on the level of psychopathology that is defined namely, the level of symptoms, syndromes or disorders. The highest comorbidity rates are observed at the symptom level. Overlap of symptoms is almost twice as high as for diagnoses (Hiller, Zaudig, & Van Bose, 1989). Clayton (1990) examined comorbidity studies from the previous 16 years and found the highest rate of 91% to occur in patients with

anxiety symptoms. Conceptual differences are most striking when syndromes are the focus of the study. Due to the use of different definitions, the comparability of such studies is limited and the comorbidity rates differ depending on the dimensional level of the syndrome (see Hiller et al., 1989).

Confusion also occurs because the diagnostic criteria and use of exclusion rules are not fully described in many studies. Some studies report rates of major depression but not the exclusion rules for such a diagnosis, which could be the presence of manic episodes, psychotic disorders, grief reactions and/or organic conditions (Wittchen, 1996). Even with the use of the DSM and ICD-10, it is often not specified whether none, some or all of the diagnostic exclusions have been considered.

Sample selection

Comorbidity rates can vary depending on the number and type of diagnostic categories considered in the study. For example, the group of anxiety disorder patients under study often includes different subtypes. As a consequence, there is little comparability between studies (see also 2.4.2). Apart from this difference in diagnostic coverage, a small sample size may create some selection bias. Comorbidity rates are found to be highest for small samples (Clayton, 1990). A selection bias also occurs when patients are recruited via advertisements or a number of selection procedures are combined (see Ball, Buchwald, Waddell, & Shekhar, 1995). Although the patients in the afore mentioned study met the DSM-III-R criteria for panic disorder with or without agoraphobia, it is questionable if the patients are representative of the population of panic disorder patients in clinical practice. Nevertheless, clinical samples are also vulnerable to selection bias. According to Bouvy (1997) inpatient samples typically include patients who have been resistant to former treatment and this treatment history, although often ignored during the evaluation of treatment outcome, clearly influences treatment response.

Time span

Comorbidity rates may also depend on the time frame of assessment: cross-sectional (two weeks, one month, six months, etc.), longitudinal (one year, three years, etc.) or lifetime (across the entire lifespan). Lifetime comorbidity rates tend to be higher than current comorbidity rates, as consistently indicated in epidemiological studies. This is partly due to the higher lifetime prevalence of disorders, when compared to the current prevalence of disorders (Kessler et al., 1996). An overview of the lifetime and current comorbidity rates for mood and anxiety disorders are presented in Table 2.1 and Table 2.2.

Table 2.1 *Epidemiological studies of comorbidity of mood and anxiety disorders*

			Major depression		Anxiety disorder	
study	assessment instrument		comorbid anxiety disorder (%) lifetime	12-months	comorbid major depression (%) lifetime	12-months
ECA	DIS (DSM-III)	any anxiety disorder	47.2	34.5[a]		26.1
		Simple phobia	25.6			
		Agoraphobia	20.4			
		Social phobia	13.6	21.7		23.7
		Panic disorder	13.0			
		OCD	14.4			
NCS	CIDI (DSM-III-R)	any anxiety disorder	58.0	51.2		
		GAD	17.2	15.4	62.4[c]	38.6[b]
		Agoraphobia	16.3	12.6	45.9[d]	
		Simple phobia	24.3	23.7	42.3[d]	
		Social phobia	27.1	20.0	37.2[d]	
		Panic disorder	9.9	8.6		
		PTSD	19.5	15.2	47.9 (men)/ 48.5 (women)[e]	
NEMESIS	CIDI (DSM-III-R)	Panic disorder		45.5		17.1
		Agoraphobia		25.5		6.7
		Simple phobia		21.8		26.2
		Social phobia		29.3		23.8
		GAD		50.3		21.9
		OCD		65.6		5.0
WHO	CIDI (ICD-10)			40		45

Note abbreviations. CIDI, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; ECA, Epidemiological Catchment Area Survey (Regier et al., 1998); NCS, National Comorbidity Survey (Kessler et al., 1996;[c]Kessler et al., 1995;[d]Magee et al., 1996;[e]Wittchen et al., 1994); NEMESIS, Netherlands Mental Health Survey and Incidence study (Ravelli et al., 1998); WHO, The WHO study on Psychological Problems in General Health Care (Lecrubier & Üstün, 1998); GAD, Generalized anxiety disorder, OCD, Obsessive compulsive disorder; PTSD, Posttraumatic stress disorder. [a] any mood disorder, [b] 30-days prevalence.

Table 2.2 *Prevalence rates of comorbidity of mood and anxiety disorders*

Authors	population	n	diagnosis	assessment	comorbid features	comorbidity rate
Ball et al., 1995	advertisement trial (N=53), referrals from mental health professionals and physicians (N=11)	64	panic disorder with/ without agoraphobia DSM-III-R	SCID (53) ADIS (11)	major depression	36%
Coryell et al., 1992	NIMH cohort (in/outpatients)	359	major depression RDC	SADS	phobia, panic attacks obsessions-compulsions	45.4%
Dilsaver et al., 1992	outpatients	42	major depression recurrent DSM-III-R	SCID	social phobia	45.2%
Fava et al., 1997	outpatients	294	major depression DSM-III-R	SCID-P	anxiety disorders social phobia social phobia simple phobia GAD panic disorder agoraphobia without panic OCD	44.9% 58% 58% 32% 16% 14% 12% 8%
Hiller et al., 1989	outpatients	150	major depression dysthymia lifetime	MDCL	symptoms syndromes (cut-off scores)	52% 29-51%

Table 2.2 (continued)

Authors	population	n	diagnosis	assessment	comorbid features	comorbidity rate
			panic disorder with/ without agoraphobia agoraphobia social phobia simple phobia GAD DSM-III-R		diagnoses	28.7%
Sanderson et al., 1990	outpatients	260	major depression (N=197) dysthymia (N=63) DSM-III-R	SCID	anxiety disorders	41.6% 47.6%
Stein et al., 1990	outpatients	63 54	social phobia panic disorder DSM-III-R	ADIS + SADS-L SADS-LA	major depression	35% (lifetime) 63% (lifetime)
Van Ameringen et al., 1991	outpatients	57	social phobia DSM-III-R	SCID-P	major depression dysthymia	70.2% 31.6%

Note abbreviations. ADIS, Anxiety Disorders Interview Schedule, Revised Version; MDCL, Munich Diagnostic Checklist; SADS, Schedule for Affective Disorders and Schizophrenia; SADS-L, Schedule for Affective Disorders and Schizophrenia-Lifetime Version; SADS-LA, Schedule for Affective Disorders and Schizophrenia-Lifetime Version for Anxiety Disorders; RDC, Research Diagnostic Criteria SCID, Structured Clinical Interview for DSM-III-R; SCID-P, Structured Clinical Interview for DSM-III-R diagnosis-Patient Edition.

The assessment instrument

The particular assessment strategy that is used is generally very critical in clinical research. More specifically, the procedure to operationalise psychiatric disorders can differ across studies from clinical diagnosis to the use of fully standardised diagnostic instruments. Standardised instruments such as the CIDI[5] produce more than twice as many diagnoses as the clinician would assign during routine diagnostic assessment (Wittchen, 1996). For this reason, comparison of studies with different assessment procedures is of limited value. Particularly when different diagnostic criteria are used and conceptual differences occur. In a review by Clayton (1990) comparing different diagnoses of panic disorder, this problem was made very clear: 'anxious neurotic' outpatients, patients with anxiety states, patients with panic and agoraphobia, patients with generalized anxiety disorder and patients with panic were all considered but in different studies.

2.4 Prevalence of comorbidity

Epidemiological studies have consistently found high comorbidity rates for psychiatric disorders and for mood and anxiety disorders in particular. About half of those people meeting the lifetime criteria for major depression also show a comorbid anxiety disorder. The one-year prevalence rates are somewhat lower than the lifetime rates (Kessler et al., 1996; Lecrubier & Üstün, 1998; Ravelli, Bijl, & Van Zessen, 1998; Regier, Rae, Narrow, Kaelber, & Schatzberg, 1998; Sartorius, Üstün, Lecrubier, & Wittchen, 1996).

Although the various anxiety disorders are highly comorbid with each other, they are equally often comorbid with mood disorders (Kessler, Zhao, Blazer, & Swartz, 1997; Lecrubier & Üstün, 1998). The National Comorbidity Survey (Kessler et al., 1996) showed different comorbidity rates per anxiety disorder, as presented in Table 2.1. Simple and social phobia coexist most in patients with major depression (lifetime and current). Comorbid mood disorders in patients with anxiety disorders (lifetime) were even more common, particularly for generalized anxiety disorder (Wittchen, Zhao, Kessler, & Eaton, 1994), agoraphobia with or without panic, simple phobia and social phobia (Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996). The current comorbidity rate was only reported for generalized anxiety disorder, which limits the comparability of this data with clinical data based on current diagnoses.

In clinical studies, the co-occurrence of panic disorder and major depression is studied most often, with comorbidity rates ranging from 10% to 70%. Restricted to current episodes, about one third of panic disorder patients show a comorbid major depression (Baldwin, 1998; Ball et al., 1995;

[5] Composite International Diagnostic Interview (WHO, 1990).

Clayton, 1990; Zajecka & Ross, 1995). In patients with social phobia, comparable rates have been observed with the social phobia mostly preceding the depression (Stein, Tancer, Gelernter, Vittone, & Uhde, 1990; Van Ameringen, Mancini, Styan, & Donison, 1991). Nevertheless, almost half of the patients with recurrent major depression show social phobia only when depressed (Dilsaver, Qamar, & DelMedico, 1992). A few clinical studies have included more than one anxiety disorder in order to compare rates across separate disorders (see Fava et al., 1997; Sanderson, Beck, & Beck, 1990). Social phobia, generalized anxiety disorder and panic disorder consistently show high comorbidity with major depression. An overview of the characteristics of the clinical studies and the observed comorbidity rates can be found in Table 2.2.

To conclude, no consistent differences have been found regarding the comorbidity of separate anxiety disorders with mood disorders. The fact that anxiety disorders show also high comorbidity with each other, further raises doubt on the relevance to study comorbidity rates of separate anxiety disorders with mood disorders. The high comorbidity rates furthermore support the relevance to study a broad range of patients with different anxiety disorders and/or mood disorders as one group.

2.5 Overlap of symptoms

Although mood and anxiety disorders appear to be different disorders in the diagnostic classification systems, overlap in their symptoms is common. In other words 'specific' anxiety symptoms and 'specific' mood symptoms often appear together in one and the same patient. Although there is no consensus on the 'specific' symptoms, the following distinction can be made, drawing partly on Clayton (1990) and Clark and Watson (1991): *Specific anxiety symptoms* include somatic anxiety, psychic anxiety and panic attacks. *Specific mood symptoms* include depressed mood, anhedonia and suicidal thoughts. *Common symptoms* include sleep and appetite disturbances, irritability, difficulty concentrating, fatigue, agitation (restlessness) and worry (ruminations). The overlap in symptoms is nevertheless not limited to the common symptoms. To illustrate, worry, psychic anxiety, somatic anxiety and the occurrence of panic attacks are also common in mood disorder patients (Fawcett, 1997).

The problem of symptom overlap in mood and anxiety disorders is best illustrated by the use of rating scales. For example, the Hamilton Rating Scale for Depression (HRSD; HAM-D) (Hamilton, 1960) is used to measure severity of depression, but also includes a number of anxiety items (e.g., psychic anxiety, somatic anxiety, agitation). These anxiety symptoms strongly correlate with the severity of the depression as measured by the total HAM-D score, moreover (Gibbons, Clark, & Kupfer, 1993). In other words,

patients with high scores on anxiety items have relatively high scores on mood items as well. In using the HAM-D, thus, severity of depression judgements is actually based on a mixture of mood and anxiety symptoms and comorbidity problems can thus arise. Due to the lack of specificity, characteristic of the rating scale, both mood and anxiety disorder patients may also obtain comparable scores on the HAM-D.

The correlations between measures of severity for anxiety and depression have also been found to be consistently high (Barbee, 1998; Bramley, Easton, Morley, & Snaith, 1988; Bouman, 1987; Frances et al., 1992). As a consequence, the ability of such measures to differentiate between mood and anxiety disorder patients is poor. The results of a meta-analysis once showed the average correlation between anxiety and depression scales to be 0.61 (Dobson, 1985). The correlations are highest for self-rating instruments and in studies with non-patient samples. Clinicians may strive (whether right or wrong) for greater discrimination in their ratings than the patients themselves. Discrimination is probably better in clinical samples, probably because of an increased frequency of severe cases (Frances et al., 1992). Frances has suggested that a strong nonspecific 'distress factor' may account for much of the overlap in mood and anxiety disorder patients.

Clark and Watson (1991) concluded, based on factor analyses, that mood disorders can best be discriminated by the presence of pervasive anhedonia while anxiety disorders can best be discriminated by the presence of somatic symptoms of hyperarousal. It is noteworthy that these physiological anxiety symptoms are most typical of panic, and not other anxiety disorders such as generalized anxiety disorder. This pattern suggests that there are very few symptoms unique to anxiety disorders when compared to mood disorders, which may also explain the lower convergent validity of anxiety scales compared to depression scales (Barbee, 1998). Beyond the specific factors of hyperarousal for anxiety and anhedonia for depression, mood and anxiety disorders share a substantial component of general affective distress. This nonspecific distress factor is called negative affect (Clark & Watson, 1991) and represents the extent to which a person is feeling upset or unpleasantly engaged as opposed to peaceful and pleasantly engaged, and it encompasses various aversive states including being upset, angry, guilty, afraid, sad or worried.

The observed covariation between mood and anxiety may thus be attributable to a shared genetic factor reflecting individual vulnerability to subjective distress and negative affect (Mineka, Watson, & Clark, 1998). Within this view, the appearance of an anxiety disorder or a mood disorder is no more than a response to a burden prompting a particular stress reaction due to a shared underlying genetic entity. The shared general distress factor can manifest itself both as a state and a more stable trait of a rather chronic nature. The general distress symptoms are met in several different diagnostic categories currently being used in clinical practice, such as in neurasthenia

(in ICD-10), adaptation disorder (in DSM) and burnout. Patients whose predominant symptoms are nonspecific (i.e., distress, demoralization, irritability, mild disturbances of sleep and appetite, distractibility and vague somatic complaints) without marked symptoms of hyperarousal or anhedonia thus may receive one of the afore mentioned 'general affective distress' diagnoses.

2.6 Sequential relationship of mood and anxiety disorders

Within a single episode, anxiety symptoms are more likely to precede depressive symptoms than the reverse (Alloy, Kelly, Mineka, & Clements, 1990). A comparable pattern is observed for lifetime comorbidity, in that anxiety disorders are signifycantly more likely to precede a mood disorder than the reverse (Alloy et al., 1990; Lepine, Wittchen, & Essau, 1993). Anxiety disorders are associated with an elevated risk of a mood disorder later in life (Kessler et al., 1997). In other words, anxiety disorders are more likely to be temporally primary to mood disorders. To illustrate, most lifetime anxiety disorders were primary disorders[6] while almost two thirds of lifetime major depressive disorders were secondary to other DSM-III-R disorders, with anxiety disorders being the most common primary condition (68%). Only about one quarter (26%) of the population reports major depressive disorder as their only lifetime disorder (pure major depression) (Kessler et al., 1996).

Coryell, Endicott, and Winokur (1992) explicitly explored the possibility of anxiety syndromes appearing within depressive episodes involving a separate disease process. The results showed the development of autonomous anxiety disorders to be rare. Patients with an initial major depression were most likely to develop a new episode of major depression. Depressive symptoms were more persistent and recurrent among patients with coexisting anxiety syndromes. Depressed patients with associated obsessions or compulsions, panic attacks or phobias were not likely to develop these symptoms as autonomous disorders during follow-up; they were much more likely to develop recurrent major depressive episodes instead.

To conclude, the diagnostic stability of primary depression has been shown to be high. Anxiety symptoms occurring within depressive episodes do not indicate a separate disorder but nevertheless have clear prognostic importance as depressed patients with any of the anxiety syndromes show poorer outcomes than those without. Once again, however, this poor outcome can not be attributed to the development of additional autonomous anxiety disorders. As Coryell et al. (1992) have therefore suggested, anxiety symptoms accompanying depression may actually be an epiphenomenon reflecting a more severe and persistent underlying illness.

[6] The primary diagnosis is defined as the diagnosis that comes first in a patient's lifetime.

2.7 Implications of comorbidity

When mood and anxiety disorders occur together, they tend to be associated with more severe symptoms, increased impairment, a more chronic illness course, poorer treatment outcome and a higher incidence of suicide (Bakish, 1999). There is consistent evidence showing mixed symptoms of mood and anxiety to reflect more severe illness (Ballenger, 1998; Barbee, 1998; Clayton, 1990; Clayton et al., 1991; Coryell et al., 1988; Coryell et al., 1992; Fawcett, 1997; Lecrubier & Üstün, 1998; Sherbourne & Wells, 1997). The probability of a new depressive episode is also increased in mood disorder patients with comorbid anxiety disorders. Comorbid panic and phobia decrease the likelihood of remission from depression (Sherbourne & Wells, 1997) and produce longer episode durations. Finally, patients with comorbid mood and anxiety disorders tend to be younger at intake and at first episode of major depression than patients with major depression alone (Coryell et al., 1992).

Comorbidity of mood and anxiety disorders consistently shows a negative correlation with treatment outcome. To illustrate, patients with major depression and panic attacks treated with antidepressants were less likely to recover during a two year follow-up than patients without panic attacks (Coryell et al., 1988). Among a group of patients with major depression, those with higher anxiety ratings took twice as long to recover from drug treatments or psychotherapy than those with lower anxiety ratings (Clayton et al., 1991). More recent studies have specifically considered the role of comorbidity of mood and anxiety disorders in treatment outcome. Fava et al. (1997) investigated the role of depressive subtypes in response to fluoxetine in outpatients with major depression and found nonanxious depressives (patients without any comorbid anxiety disorder) to improve more during treatment than anxious depressives, while other subtypes did not show differences in treatment outcome. The presence or absence of comorbid anxiety in inpatients with severe major depression made no difference to treatment outcome (Rodney et al., 1997). As noted before, however, selection bias obviously occurs in inpatient samples (Bouvy, 1997) which is reflected in the results.

Finally, severe anxiety symptoms and particularly when associated with major depression appear to constitute an acute risk factor for suicide (Angst, Angst, & Stassen, 1999; Fawcett, 1997; Lecrubier & Üstün, 1998). Suicidal ideation, a history of past suicide attempts and the severity of hopelessness have not found to correlate significantly with suicide over the subsequent year but the severity of psychic anxiety and the presence of panic attacks do correlate significantly. Rapid and aggressive treatment of symptoms of anxiety/agitation symptoms with suitable antidepressants or benzodiazepines should thus be considered to reduce the acute risk of suicide (Fawcett, 1997).

3 The personality model of Cloninger

The personality model of Cloninger (Cloninger, 1987) has been reputed to differentiate between responders and nonresponders to antidepressant treatment. In the present study, the model is therefore included to explore the differential responses of patients with mood and/or anxiety disorders to antidepressant treatment (e.g., TCA versus SSRI). In the present chapter, the theoretical model and corresponding inventory, the Tridimensional Personality Questionnaire (TPQ), will be considered in greater detail. Thereafter, the relevance of the personality model will be considered from two perspectives: the underlying theoretical assumptions regarding temperament and the psychopathology of mood and anxiety disorders (3.2) and the empirical support for the role of temperament in antidepressant treatment response (3.3).

3.1 The personality model of Cloninger

Cloninger has developed a general model of personality that applied to both normal and abnormal personality (Cloninger, 1987; Cloninger, Svrakic & Przybeck, 1993). The existing personality models were focused on either normal personality in terms of trait dimensions or abnormal personality in terms of the classification of personality disorders. Although in both areas of research, three dimensions or clusters of characteristics have been found to arise, no systematic relationship has been described between both areas. Cloninger described not only the observed structure of personality (phenotype), as in the model of Eysenck (Neuroticism-Extraversion-Psychoticism), but also included the underlying biogenetic structure (genotype). Eysenck assumed that phenotypic structure and genotypic structure were the same although this is questionable, according to Cloninger. To illustrate, extraversion has been found to be genetically heterogeneous; that is, extraversion appears to be composed of the two genetically independent factors of impulsivity and sociability which constitute a single behavioural dimension due to shared environmental influences. In addition, anti-anxiety drugs have been found to reduce not only scores on neuroticism but also on introversion, which suggests that these dimensions of personality share biological determinants even though they are typically assumed to represent independent processes (Cloninger, 1987). Yet another illustration of the limited value of traits for the assessment of personality disorder is the content of the factor called neuroticism which is a clinically heterogeneous composite of anxiety, hostility, depression, self-consciousness, impulsiveness and general emotional vulnerability. High neuroticism scores are frequent for individuals with a personality disorder but also for many psychiatric patients without a perso-

nality disorder; even some people with no psychiatric disorder have high neuroticism scores (Cloninger et al., 1993).

On the basis of foregoing types of evidence, Cloninger concluded that personality factors are clinically and genetically heterogeneous and therefore inadequate for understanding the underlying determinants of psychopathology. In order to test a number of hypotheses about the causal structure of personality, Cloninger developed a general psychobiological model of personality in which the psychosocial and neurobiological approaches to patient assessment and treatment are integrated (Cloninger, 1987). The original model included three dimensions of temperament postulated to be genetically homogeneous and independent of each other: *Novelty Seeking, Harm Avoidance* and *Reward Dependence*. More recently, the model has been extended to include seven factors pertaining to temperament and character[7]. Temperament involves individual differences in automatic emotional reactions and habits, character involves differences in self-concepts about goals and attitudes. Cloninger defined *personality* as "*differences between individuals in the adaptive systems involved in the reception, processing, and storing of information about experience*" (Cloninger et al., 1993). Although the model was extended to be more comprehensive and improve the diagnosis of personality disorders, temperament continues to be of primary interest in the search for the biological determinants of mood and anxiety disorders. Dimensions of temperament appear to be more directly tied to the neurobiological and genetic determinants of behaviour than dimensions of character, so the model of temperament will therefore be the focus of the present study and described in greater detail below.

3.1.1 The model of temperament

The temperament dimensions are defined in terms of individual differences in associative learning in response to novelty, danger or punishment and reward (see Figure 3.1). Each dimension of temperament has been hypothesised to reflect the underlying biogenetic structure of an individual in terms of variations of the dopaminergic, serotonergic and noradrenergic brain systems.

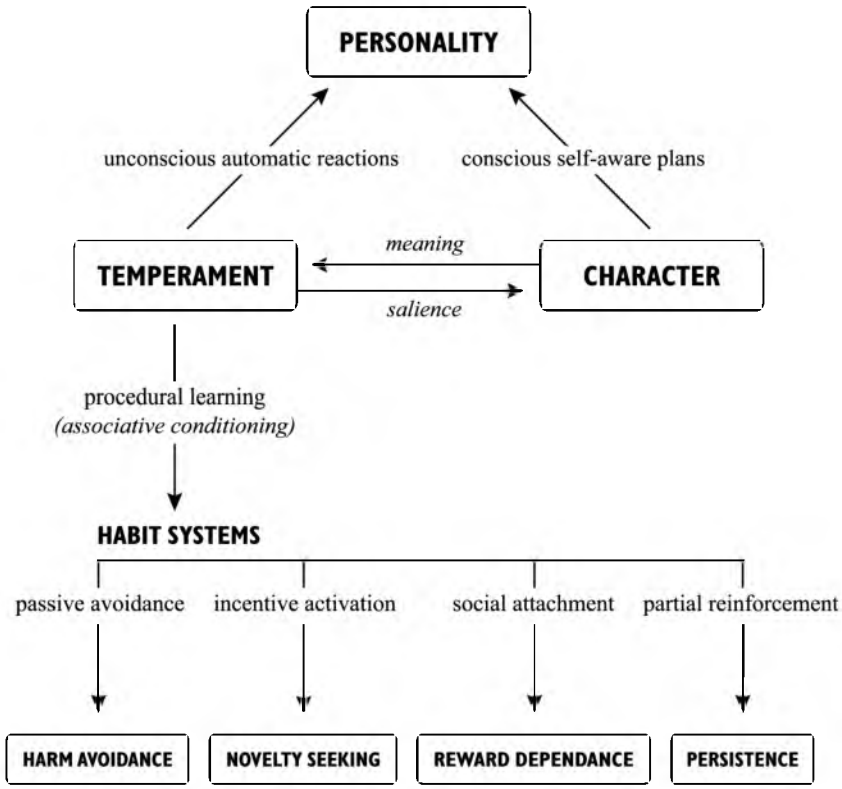
Novelty Seeking is viewed as a heritable bias towards the activation or initiation of behaviour, which may include frequent exploratory activity in response to novelty, impulsive decision making, quick loss of temper and active avoidance of monotony and frustration. Dopaminergic projections from the ventral tegmental area in the brainstem to the striatum (caudate and putamen) and other limbic and cortical sites are predicted to play a crucial role in

[7] *Persistence* was originally a subscale of reward dependence and is now recognised as an independent dimension. Three additional character dimensions are: *self-directedness, cooperativeness* and *self-transcendence*.

the neuromodulation of behavioural activation in response to novelty and to signals of reward.

Harm Avoidance is a heritable tendency to respond intensely to signals of aversive stimuli, which may include the inhibition of behaviour to avoid punishment, the avoidance of novelty and the avoidance of frustrative nonreward. Examples of such a behavioural inhibition pattern are: pessimistic worry in anticipation of future problems, such passive avoidant behaviours as a fear of uncertainty and a shyness of strangers, and rapid fatigability. Serotonergic, noradrenergic and cholinergic projections to the amygdala and septohippocampal regions underlying the temperal cortex are predicted to play a crucial role in the neuromodulation of behavioural inhibition in response to signals of punishment or non-reward.

Reward Dependence is viewed as a heritable bias towards the maintenance or continuation of ongoing behaviours which can manifest itself as sentimentality, social attachment and dependence on the approval of others. Individual differences in postsynaptic sensitivity of neurons in the frontal cortex to noradrenergic projections from the locus ceruleus in the brainstem are predicted to play a role in reward dependence.



Source: Cloninger unpublished (1996)

Figure 3.1 *Model of temperament*

Persistence, was originally taken to be a component of Reward Dependence but emerged as a separate fourth dimension measured in terms of perseverance despite frustration and fatigue. Persistence is predicted to reflect individual differences in the brain's systems for the modulation of intermittent reinforcement. Signals of intermittent punishment are converted into signals of eventual reward by short-circuiting activation of the behavioural inhibition system and thereby stimulating the behavioural activation system which depends on crucial projections from the hippocampal subiculum (part of the inhibition system) and the nucleus accumbens (part of the activation system).

These four dimensions of temperament are assumed to be heritable, manifest themselves early in life and involve unconscious biases in learning. Large-scale twin studies have shown the heritability of the dimensions between 50% and 65% and confirmed that the dimensions were genetically homoge-

neous and independent (Heath, Cloninger, & Martin, 1994; Stallings, Hewitt, Cloninger, Heath, & Eaves, 1996). In both normal and abnormal samples, the dimensions of temperament have been found to be highly reliable and stable despite mood state. Only Harm Avoidance has been found to increase when patients are agitated or distressed (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). Unfortunately, the relation of temperament to regional brain activity is difficult to assess because the networks of brain connections are very complicated. Cloninger found support for a number of his neurobiological predictions using brain imaging, neurocognitive, neurochemical and neuroendocrine measures (Cloninger et al., 1994). Nevertheless, the empirical evidence regarding the relations of temperament to variations in the dopaminergic, serotonergic and noradrenergic brain systems is still quite limited. Empirical evaluation of the specific relations between the neurotransmission brain systems and temperament is beyond the scope of the present thesis, moreover.

3.1.2 The Tridimensional Personality Questionnaire (TPQ)

The Tridimensional Personality Questionnaire was developed to operationalise the theoretical construct of temperament (Cloninger, 1987; Cloninger, Przybeck, & Svrakic, 1991). This selfreport inventory consists of 100 true-false items and originally measured three dimensions of temperament: Novelty Seeking (NS), Harm Avoidance (HA) and Reward Dependence (RD) with each scale consisting of four subscales (see Table 3.1). As already noted, however, normative studies using the TPQ showed Persistence to be uncorrelated with other aspects of Reward Dependence and to therefore constitute an independent dimension of temperament: Persistence (P) (Cloninger et al., 1993). The TPQ is the precursor to the Temperament and Character Inventory (TCI)[8] (Cloninger et al., 1994) and the psychometric properties of the TCI have been best described. The correlations between the TPQ and TCI temperament scale scores have been found to be high (.971 for NS, .997 for HA, .932 for RD and .883 for P) and the TCI scales have been found to be moderately to highly reliable. The internal consistency of the scales, as measured by Cronbach's alpha has been found to range from .65 for P to .87 for HA. The test-retest reliability of the scales has been found to range from .54 for HA to .72 for P in an inpatient population and range from .71 for RD to .79 for NS in an outpatient population. The reliability of the TPQ has not been considered separately.

[8] The TCI assesses seven dimensions of personality and consists of 240 items, including 90 original TPQ items.

Empirical validation of the TPQ rests, rather, on the strong association of eight temperament types (combinations of NS, HA and RD)[9] with the DSM-III-R clusters of personality disorders in adults (Svrakic, Whitehead, Przybeck, & Cloninger, 1993; Goldman, Skodal, Mc Grath, & Oldham, 1994). In addition, longitudinal studies have shown a childhood configuration of high NS, low HA, low RD and low P to predict adolescent antisocial behaviour, alcohol and drug abuse and adult criminality (Cloninger et al., 1994). When Stallings et al. (1994) carried out a structural analysis of the underlying genetic and environmental antecedents of the TPQ in a large population of twins, moreover, the results also showed the different dimensions of temperament to be genetically homogeneous and genetically independent of each other.

The TPQ has been translated and studied in several countries and is also avialable in Dutch. Psychometric data based on a normal Dutch population is available for only the TCI, however (Duijsens, Goekoop, J.G., Spinhoven, P., & Eurelings-Bontekoe, 1997). The mean scores for HA and RD were found to be significantly higher than the scores from an American sample: 15.15 versus 12.6 and 16.14 versus 15.4, respectively. The mean score for P was significantly lower with 4.19 versus 5.6. The internal consistency of the scales was comparable to that for the American sample (Cloninger et al., 1994).

3.2 The relation of temperament to mood and anxiety disorders

The different dimensions of temperament appear to be closely related to a differential susceptibility to neurotic syndromes (Cloninger et al., 1993). Different levels of Harm Avoidance are hypothesised to reflect variations in the brain's behavioural inhibition system. An intense response to signals of aversive stimuli and an associated tendency to inhibit behaviour in order to avoid punishment, novelty or the frustration of nonreward will lead to a passive avoidance pattern of behaviour. In addition to this, high Harm Avoidance is hypothesised to increase susceptibility to mood and anxiety disorders and empirical findings have indeed shown consistently elevated Harm A-

[9] The subtypes of personality disorders can be largely understood in terms of the interaction of the different dimensions of temperament (called temperament types).Temperament scores are grouped into low, average or high categories (of equal size in terms of percentile scores) to create eight extreme temperament types which also correspond to the traditional personality categories found in the DSM. Everyone can be assigned to one temperament type. In contrast, the DSM system often shows overlap in diagnoses due to a lack of specificity of the diagnostic criteria. The test-retest reliability of the temperament types has been found to be moderately high (.75) (Cloninger et al., 1994) and the stability was best for the severe cases.

voidance scores in patients with mood and anxiety disorders when compared to the normal population (Brown, Svrakic, Przybeck, & Cloninger, 1992; Cloninger et al., 1994; Cowley, Roy-Byrne, Greenblatt, & Hommer, 1993; Joffe, Bagby, Levitt, Regan, & Parker, 1993). Individuals with various anxiety disorders are also expected to score high on Harm Avoidance and have consistently been found to do so. However, individuals with high Harm Avoidance do not necessarily show an anxiety disorder, that is, they may be healthy or demonstrate some other form of psychopathology (e.g., major depression). In addition, high Novelty Seeking was found to be related to a lower sedation stresshold or, in other words, greater sensitivity to sedation. Compliance with drug taking was also found to be lower for anxiety disorder patients with high Novelty Seeking (Cloninger et al., 1994).

According to Cloninger's theory, Harm Avoidance is assumed to be directly related to a susceptibility to anxiety disorders, while the different subtypes of depression are assumed to be related to different interactions between temperaments. Empirical studies have indeed shown Harm Avoidance scores to be consistently elevated in patients with mood disorders when compared to the general population (Cloninger et al., 1994). Furthermore, the assumption that high Novelty Seeking in combination with high Harm Avoidance will lead to dysthymia due to a continuous approach-avoidance conflict within the individual (i.e., an imbalance between behavioural activation and inhibition) has been supported. Conversely, impulsive-aggression is expected when high Novelty Seeking is combined with low Harm Avoidance. In addition, people with high Reward Dependence scores are predicted to be sensitive to social loss, which can lead to the reactive dysphoria characteristic of atypical depression (Cloninger et al., 1994).

A crucial question is whether elevated temperament scores reflect lifelong personality traits or state mood. Harm Avoidance has been found to be related to current mood state, while the other dimensions of temperament show much less sensitivity to changes in mood state. Harm Avoidance scores are less stable in depressed patients than in the general population (test-retest correlations of .79 versus .51) and Harm Avoidance scores have been shown to covary with changes in mood measured before and after treatment (Brown et al., 1992). In panic disorder patients, however, Harm Avoidance scores have been found to remain stable, despite reductions in panic attacks, which suggests that Harm Avoidance may increase during acute depressed states but constitutes a stable feature of many anxiety disorders (Cloninger et al., 1994).The finding that both mood and anxiety disorder patients score high on Harm Avoidance raises the question of how to discriminate susceptibility to these disorders. At this point, more research is needed. The discriminant validity of the TCI with regard to anxiety and depression shows anxiety to be solely related to high Harm Avoidance while depression is related to a combination of high Harm Avoidance and high Novelty Seeking (Cloninger et al., 1994). These findings are in line with the assumption that

anxiety is directly related to Harm Avoidance, while depression is influenced by the interaction of the different dimensions of temperament.

3.3 Temperament and antidepressant treatment response

Several studies have explored the role of temperament as a possible predictor of antidepressant treatment response. Joffe et al. (1993) showed outpatients who were nonresponders to standard antidepressant treatment[10] for major depression to score higher on Harm Avoidance than responders at both baseline and after three months of treatment. In another study, specific combinations of temperaments (temperament types) have been related to response to antidepressants (Joyce, Mulder, & Cloninger; 1994). In fact, temperament type turned out to be the only predictor of outcome when compared to personality disorder, severity of depression, age and sex, and it accounted for 25% of the variance. Patients with low scores on all three dimensions of temperament and patients with high Harm Avoidance combined with high Reward Dependence showed a high response rate to antidepressants (desipramine and clomipramine). Patients with high scores on Novelty Seeking but low scores on the other dimensions of temperament and patients with high scores on Harm Avoidance and low scores on Reward Dependence or visa versa showed low treatment response. Cloninger concludes that depressives are clinically and etiological heterogeneous and that temperament is a more powerful way of characterising this heterogeneity than variation in depressive symptoms or comorbid psychopathology (Cloninger et al., 1994). More recently, Nelson and Cloninger (1997) showed that patients with major depression and high scores on Reward Dependence showed lowest response to antidepressants (nefazodone). In line with previous findings, Harm Avoidance, Reward Dependence and their interaction predicted treatment response. It should be noted that the model showed a significant predictive value due to the large number of patients but only accounted for 1.1% of the variance in the results. Nelson and Cloninger therefore conclude that although the clinical utility of these findings is uncertain, such a line of investigation nevertheless constitutes a potentially useful strategy for linking temperament to pharmacological response.

As shown, the role of temperament in antidepressant treatment response has been studied primarily in patients with a mood disorder. In a study of the treatment of patients with a panic disorder or generalized anxiety disorder (Wingerson et al., 1993), it was found that dropouts scored significantly

[10] Standard treatment involved initial trial on imipramine or desipramine for five weeks. Initial failures then received augmentation with lithium, triiodothyronine or both, an SSRI, and then after washout a monoamine oxidase inhibitor (Joffe et al., 1993).

higher than completers on Novelty Seeking; other demographic and clinical variables, moreover, did not differentiate dropouts from completers.

To summarise: there is considerable empirical evidence that high Harm Avoidance is consistently related to a nonresponse to antidepressant treatment. Temperament type has also been found to be related to treatment response although the predisposing role of certain temperament types (e.g., high Harm Avoidance/high Novelty Seeking or high Harm Avoidance/high Reward Dependence) has yet to be demonstrated. More replication studies are certainly needed. The personality model of Cloninger provides a new perspective on the identification of patients within the broad spectrum of mood and anxiety disorders. Rather than a focus on the DSM categories based on current symptomatology, the psychobiological model of Cloninger provides an alternative typology of patients based on temperament dimensions. Such a personality approach, linked to underlying neurobiological structures, may be particularly useful for the detection of differences in antidepressant treatment response.

4 Outline of the empirical research

The aim of the present study was to explore possible, previously undetected, differences between antidepressants. The comorbidity between mood and anxiety disorders raises problems for accurate diagnosis and thereby problems for the selection of patients in outcome research. In recognition of such comorbidity problems and to reduce selection bias, we therefore chose a design different from that used in previous clinical trials: All patients who might benefit from antidepressant treatment were included - both patients with mood as well as anxiety disorders. The study design and selection procedures will be considered in greater detail below.

4.1 Overall study outline

At three study sites, all new outpatients were screened for inclusion in the study. Patients were screened by the treating psychiatrist at intake for the presence of a mood or anxiety disorder, for the absence of exclusion conditions and for the severity of the pathology. Subsequent assessment of those patients considered eligible was then done by an independent rater both at baseline and during treatment.

4.2 Participating centres

The participating centres were a community mental health centre (RIAGG Dordrecht: centre 1), an outpatient clinic affiliated with a psychiatric hospital (Delta Hospital, Multifunctional Centre Rotterdam-South: centre 2) and an outpatient clinic affiliated with a general hospital (Hospital Velp: centre 3). The centres were all situated in the Netherlands. Data collection took place between May 1994 and October 1996 and was initiated at the RIAGG Dordrecht, followed by centre 2 in January 1995 and centre 3 in May 1995.

4.3 Study design

The study was an open, randomised, 6-week treatment study to compare imipramine and fluvoxamine. One of the aims of the study was to include a sample as representative of normal clinical practice as possible. A double blind design was considered unsuitable as we anticipated serious bias due to the refusal of certain patients to participate. Knowing what medication they are taking appears to be important to patients, and the conditions for providing one's informed consent appear to be easier to accept under such cir-

cumstances. Non-blindness is nevertheless a disadvantage for researchers due to possible judgement biases during the evaluation of treatment outcome. In order to reduce the bias possibly introduced by non-blind experimental treatment, the outcome ratings were performed by a person blind to treatment condition.

4.4 Inclusion criteria

All new attending patients were screened using the following inclusion criteria.

1. Age between 18 and 65 years.
2. Current diagnosis with a mood or anxiety disorder according to the DSM-III-R criteria as assessed using the Munich Diagnostic Checklist (MDCL: Hiller, Zaudig & Mombour, 1990).
3. At least a moderate illness severity on the Clinical Global Impression (CGI: Guy, 1976).
4. Provision of informed consent.

To facilitate selection of a broad diagnostic group of patients and encourage application of a systematic diagnostic procedure, we semi-structured the MDCL by selecting the relevant checklists to be completed at screening. A subset of 14 checklists was used: adjustment disorder, agoraphobia, alcohol dependence and abuse, bulimia nervosa, cyclothymia, dysthymia, generalized anxiety disorder, major depressive disorder, obsessive compulsive disorder, panic disorder with and without agoraphobia, schizoaffective disorder, simple phobia and somatization disorder (see also Chapter 5, pp. 59; Chapter 6, pp. 70).

4.5 Exclusion criteria

1. Unsuccessful treatment with an accurate dose and accurate duration of fluvoxamine or imipramine during this episode.
2. Pregnancy, lactation or females with childbearing potential not using adequate contraception.
1. History of epilepsy or seizures.
4. Clinically important or unstable disease, or some other disease which could interfere with the diagnosis or treatment of depression.
5. Liver or kidney disease.
6. Patients with clinically relevant abnormal laboratory test results.
7. Cardiovascular insufficiency, AV-block grade I-III, arrhythmia, recent myocardial infarction, prolonged cardiac conduction times.
8. Adrenal tumours (pheochromocytoma, neuroblastoma).
9. Miction disturbances, prostate hypertrophy, glaucoma.

10. Multiple drug allergies.
11. Treatment with an experimental drug, a MAOI, lithium, antipsychotic or electroconvulsive shock therapy (ECT) within two weeks of entering the study.
12. Treatment with an antidepressant within one week of randomisation and fluoxetine within five weeks of entering the study.
13. Concurrent use of central nervous system (CNS) medication, other than for nighttime sedation and to control anxiety.
14. Patients with language or understanding difficulties which make assessment impossible or difficult.
15. Patients previously enrolled in this study.
16. Use of cocaine, amphetamine or opiates, or daily use of alcohol (more than 3 drinks a day).

4.6 Size of the patient samples

A total of 114 patients were included and randomised to one of the treatment conditions. After randomisation and before initiation of treatment, five patients refused to participate further and one patient turned out to meet one of the exclusion criteria. A total of 108 patients thus participated in the treatment study. Most of the patients were admitted to the RIAGG Dordrecht: a total of 92 patients (85%). Six patients were included from the Delta Hospital Rotterdam, and a total of ten patients from the Hospital Velp were included (see Table 4.1).
Given that most of the multi-centre patient sample came from the RIAGG Dordrecht population, we decided to use only this patient sample to study the efficacy of treatment. The principal argument for not including the patients from the other centres in this analysis was that our goal of obtaining a multi-centre sample including a variety of patients in different treatment settings was not met. The efficacy results would therefore be determined primarily by the RIAGG Dordrecht sample.

The question of diagnostic accuracy, in contrast, can be studied using the multi-centre sample. The selection procedure in the present study is not assumed to interfere with the comparison of diagnostic procedures (clinical diagnosis versus structured diagnostic interview).

Table 4.1 *Demographic and clinical characteristics per centre*

	Centre 1 RIAGG Dordrecht		Centre 2 Delta Hospital Rotterdam		Centre 3 Hospital Velp	
	M	*SD*	*M*	*SD*	*M*	*SD*
Age[a]	34.50	9.94	52.19	11.79	33.01	9.48
	n	*%*	*n*	*%*	*n*	*%*
Patient sample	96		6		10	
Sex[b]						
male	33	35.9	2	33.3	5	50.0
female	59	64.1	4	66.7	5	50.0
Marital status[c]						
married	40	43.5			6	60.0
never married	38	41.3	2	33.3	4	40.0
divorced	13	14.1	3	50.0		
widowed	1	1.1	1	16.7		
Education[d]						
elementary school	36	39.1	4	66.7	7	70.0
high school	42	45.7	1	16.7	1	10.0
higher	14	15.2	1	16.7	2	20.0
Treatment medication[e]						
fluvoxamine	48	52.2	2	33.3	5	50.0
imipramine	44	47.8	4	66.7	5	50.0
MDCL diagnosis[f]						
Mood disorder (M)	20	21.7	3	50.0	3	30.0
Anxiety disorder (A)	46	50.0	3	50.0	6	60.0
Comorbid M-A	26	28.3			1	10.0
CIDI diagnosis[g]						
Mood disorder (M)	18	22.2	1	16.7	2	22.2
Anxiety disorder (A)	19	23.5	2	33.3	4	44.4
Comorbid M-A	41	50.6	3	50.0	3	33.3
No diagnosis	3	3.7				

Note. [a] $F(2,108) = 9.12$, $p < .05$; [b] $\chi^2(2,108) = .81$, $p > .05$; [c] $\chi^2(6,108) = 17.49$, $p < .05$; [d] $\chi^2(4,108) = 6.61$, $p > .05$; [e] $\chi^2(2,108) = .80$, $p > .05$; [f] $\chi^2(4,108) = 4.99$, $p > .05$. [g] $\chi^2(6,96) = 2.63$, $p > .05$

The analyses for the different research questions are thus based on different patient samples and sample sizes. An overview of the different samples is presented in Figure 4.1, and the selection procedures for the separate research studies will be described in greater detail below.

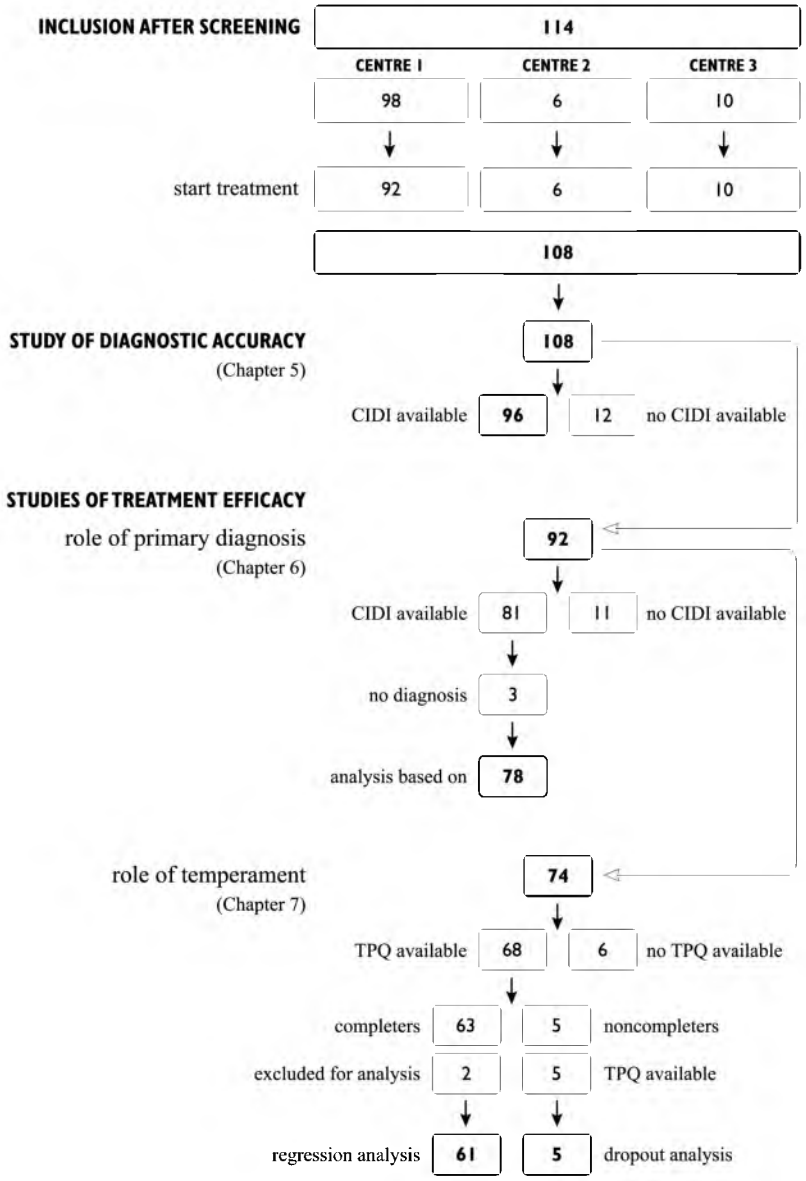


Figure 4.1 *Selection of the patient samples*

For the *study of diagnostic accuracy* (see Chapter 5), the multi-centre sample was analysed. A total of 108 patients started treatment (centre 1: 92 patients; centre 2: 6 patients; centre 3: 10 patients). For 96 of these patients, CIDI data was available. Because the CIDI was assessed during week 4 of treatment, patients who dropped out before week 4 would not be assessed. In order to obtain the CIDI data for the entire sample, the patients dropping out before week 4 were nevertheless asked to complete the CIDI. The procedure was that the treating psychiatrist contact the researcher as soon as possible when a patient did not complete the treatment study. The researcher then phoned the patient to request further co-operation on the remaining assessments. The reasons for noncompletion of the treatment were as follows: non-compliance with treatment (4 patients), non-compliance with the study (4 patients) and serious side effects (4 patients). For a few patients, the psychiatrist recommended not contacting them for further co-operation because the patient stated that they did not want to participate any longer. The other patients were telephoned, and one patient was sent a letter because telephone contact was not possible. They all refused to co-operate further, however.

A comparison of the clinical diagnosis with the CIDI diagnosis was thus available for 96 (or 89%) of the 108 patients. The demographic characteristics of the 12 patients with no CIDI diagnosis showed no significant differences when compared to the sample of 96 patients, with the exception of educational level ($\chi^2(2,108) = 6.02$, $p = .05$) (see Table 4.2).

More of the patients who dropped out had only an elementary education when compared to those who did not drop out. Furthermore, the MDCL-based diagnoses (including mood disorder, anxiety disorder or comorbid mood and anxiety disorders) for the patients who dropped out were comparable to those for the 96 patients who participated ($\chi^2(2,108) = 2.05$, $p > .05$).

Table 4.2 *Demographic and clinical characteristics of the analysed patient sample (n=96) versus excluded cases (n=12) for the study of diagnostic accuracy (Chapter 5)*

	Patient sample (n=96)		Excluded cases (n=12)	
	M	*SD*	*M*	*SD*
Age[a]	35.98	10.92	30.23	7.56
	n	%	*n*	%
Sex[b]				
male	36	37.5	4	33.3
female	60	62.5	8	66.7
Marital status[c]				
married	40	41.7	6	50.0
never married	40	41.7	4	33.3
divorced	14	14.6	2	16.7
widowed	2	2.1		
Education[d]				
elementary school	38	39.6	9	75.0
high school	41	42.7	3	25.0
higher	17	17.7		
Treatment medication[e]				
fluvoxamine	50	52.1	5	41.7
imipramine	46	47.9	7	58.3
MDCL diagnosis[f]				
Mood disorder (M)	25	26.0	1	8.3
Anxiety disorder (A)	47	49.0	8	66.7
comorbid M-A	24	25.0	3	25.0

Note. [a] $t = -1.77$, $p > .05$; [b] $\chi^2(1,108) = .08$, $p > .05$; [c] $\chi^2(3,108) = .64$, $p > .05$; [d] $\chi^2(2,108) = 6.02$, $p = .05$; [e] $\chi^2(1,108) = .46$, $p > .05$; [f] $\chi^2(2,108) = 2.05$, $p > .05$

For *the study of the role of primary diagnosis in the efficacy of antidepressant treatment*, we used the RIAGG Dordrecht sample exclusively (see Chapter 6). A total of 98 patients were included and randomised to one of the treatment conditions. However, before initiation of the treatment, five pa-

tients refused to participate further and one patient turned out to meet one of the exclusion criteria, which produced a final RIAGG Dordrecht sample of 92 patients.

For 81 of the 92 patients, the CIDI data were available to operationalise the diagnosis at first episode or the primary diagnosis. Three of the patients had no DSM diagnosis according to the CIDI (see above), which meant that the analyses of the role of primary diagnosis in the efficacy of antidepressant treatment involved a total of 78 patients. The 14 patients who were not included in the efficacy analyses showed no significant differences with regard to demographic characteristics or clinical characteristics when compared to the 78 patients who were included, with the exception of completion of the 6-week treatment ($\chi^2(1,92) = 46.92$, $p < .001$). The excluded sample consisted of more noncompleters than the included sample (see Table 4.3).

A total of 15 patients did not complete the 6-week treatment. For the four patients who dropped out after 4 weeks of treatment, the CIDI-based diagnosis was available. Of the 78 patients included in the analyses, 74 patients completed the treatment and four patients thus did not complete the 6-week treatment. Although the demographic characteristics were comparable for both groups, the exclusion of 14 patients from the analyses of treatment efficacy may nevertheless have introduced a selection bias because we cannot assume the two groups of patients to be equivalent with regard to diagnostic, clinical and personality characteristics.

Table 4.3 *Demographic and clinical characteristics of the analysed patient sample versus excluded cases for study of the role of primary diagnosis in the efficacy of treatment (Chapter 6)*

	Patient sample (n=78)		Excluded cases (n=14)	
	M	*SD*	*M*	*SD*
Age[a]	35.05	10.03	31.45	9.15
	n	*%*	*n*	*%*
Sex[b]				
male	27	34.6	6	42.9
female	51	65.4	8	57.1
Marital status[c]				
married	34	43.6	6	42.9
never married	33	42.3	5	35.7
divorced	10	12.8	3	21.4
widowed	1	1.3		
Education[d]				
elementary school	27	34.6	9	64.3
high school	37	47.4	5	35.7
higher	14	18.0		
Treatment medication[e]				
fluvoxamine	42	53.8	6	42.9
imipramine	36	46.2	8	57.1
Treatment completers[f]				
completers	74	94.9	3	21.4
dropouts	4	5.1	11	78.6
MDCL diagnosis[g]				
Mood disorder (M)	19	24.4	1	7.1
Anxiety disorder (A)	36	46.2	10	71.4
comorbid M-A	23	29.5	3	21.4

Note. [a] $t = -1.25$, $p > .05$; [b] $\chi^2(1,92) = .35$, $p > .05$; [c] $\chi^2(3,92) = .93$, $p > .05$; [d] $\chi^2(2,92) = 5.54$, $p > .05$; [e] $\chi^2(1,92) = .57$, $p > .05$; [f] $\chi^2(1,92) = 46.92$, $p < .001$; [g] $\chi^2(2,92) = 3.41$, $p > .05$

For *the study of the role of temperament in the differentiation of antidepressant treatment response*, a subsample (74 patients) of the RIAGG Dordrecht sample of 92 patients was used (see Chapter 7). At the start of the research project, we administered the TPQ at baseline. In light of the fact that our patient population reported considerable difficulty with the completion of the TPQ and the fact that the TPQ has been designed to assess dimensions of temperament which are relatively stable over time (Cloninger, 1987), we decided to administer the TPQ at week 6 of treatment in stead of baseline to the remaining 74 patients. The TPQ was designed to assess a person's habitual feelings and behaviour independent of the current period because temperament is assumed to not change over time. That is, temperament refers to automatic emotional responses which have been found to be moderately heritable (Heath, Cloninger, & Martin, 1994) and stable throughout life (Cloninger, 1987; Cloninger, Przybeck, Svrakic, & Wetzel, 1994). At the same time, however, considerable doubt has been raised about the stability of temperament, and especially Harm Avoidance scores have been found to vary depending on the current mood state (Brown, Svrakic, Przybeck, & Cloninger, 1992; Joffe et al., 1993). Additional evidence has also been raised more recently with regard to a lack of stability for the Harm Avoidance scale (Chien & Dunner, 1996) (see also Chapter 7, pp.90; Chapter 8, pp. 100-01). The 18 patients who were scheduled to complete the TPQ at baseline were not included in the final analyses to prevent possible bias due to different assessment points. In other words, the analyses were restricted to a subsample of 74 patients who completed the TPQ after 6 weeks of treatment.

For the relevant subsample, no significant differences with regard to demographic or clinical characteristics were found when compared to the other cases treated at the RIAGG Dordrecht (see Table 4.4).

Sixtyeight patients (or 92%) of the 74 patients completed the TPQ. The 63 patients who completed the 6-week treatment all completed the TPQ. The 11 patients who did not complete the 6-week treatment were asked by phone to still complete the TPQ, which was then mailed to them. Five of the 11 patients then completed the TPQ, all within four weeks after dropout. Five patients, however, refused to cooperate further and one patient never returned the questionnaire. To conclude, in six of the 74 patients the TPQ data were not available, which may have introduced a selection bias.

Table 4.4 *Demographic and clinical characteristics of the subsample of the RIAGG Dordrecht sample (n=74)) for study of the role of temperament in the efficacy of treatment versus the other cases of the RIAGG Dordrecht sample (n=18) (Chapter 7)*

	Patient sample (n=74)		Other cases (n=18)	
	M	*SD*	*M*	*SD*
Age[a]	34.86	10.18	33.02	8.95
	n	*%*	*n*	*%*
Sex[b]				
male	28	37.8	5	27.8
female	46	62.2	13	72.2
Marital status[c]				
married	32	43.2	8	44.4
never married	30	40.5	8	44.4
divorced	11	14.9	2	11.2
widowed	1	1.4		
Education[d]				
elementary school	26	35.1	10	55.6
high school	35	47.3	7	38.9
higher	13	17.6	1	5.5
Treatment medication[e]				
fluvoxamine	36	48.6	12	66.7
imipramine	38	51.4	6	33.3
Treatment completers[f]				
completers	63	85.1	14	77.8
dropouts	11	14.9	4	22.2
MDCL diagnosis[g]				
Mood disorder (M)	17	23.0	3	16.7
Anxiety disorder (A)	36	48.6	10	55.6
Comorbid M-A	21	28.4	5	27.8
CIDI diagnosis[h]				
Mood disorder (M)	14	21.5	4	25.0
Anxiety disorder (A)	14	21.5	5	31.3
Comorbid M-A	34	52.3	7	43.8
No diagnosis	3	4.6		

Note. [a] $t = -.70$, $p > .05$; [b] $\chi^2(1,92) = .64$, $p > .05$; [c] $\chi^2(3,92) = .45$, $p > .05$; [d] $\chi^2(2,92) = 3.14$, $p > .05$; [e] $\chi^2(1,92) = 1.88$, $p > .05$; [f] $\chi^2(1,92) = .57$, $p > .05$; [g] $\chi^2(2,92) = .41$, $p > .05$; [h] $\chi^2(3,81) = 1.51$, $p > .05$

Based on the data control procedures (also see Chapter 7, pp. 86) we decided that outcome data collected more than two weeks difference from week 6 of treatment would be excluded from further analyses. Two patients were therefore excluded from the regression analysis for the role of temperament in treatment. The relevant regression analysis was thus based on 61 patients in the end. The patients in this subsample showed no significant differences with regard to demographic characteristics when compared to the other patients, with the exception of educational level ($\chi^2(2,74) = 6.16$, $p < .05$) (see Table 4.5).

Furthermore, their clinical characteristics showed no significant differences, with the exception of treatment completion $\chi^2(1,74) = 60.63$, $p < .001$). Inherent to the regression procedure, the analysed group consisted of patients who completed treatment. The noncompleters were therefore analysed separately because - as mentioned before - 5 of the 11 patients who did not complete treatment still completed the TPQ. The analysis of the noncompleters was therefore limited to 5 patients.

Table 4.5 *Demographic and clinical characteristics of sample included in TPQ regression analyses (n=61) versus other cases (n=13) (Chapter 7)*

	Analysed sample (n=61)		Other cases (n=13)	
	M	*SD*	*M*	*SD*
Age[a]	35.69	10.45	33.92	8.05
	n	%	*n*	%
Sex[b]				
male	24	39.3	4	30.8
female	37	60.7	9	69.2
Marital status[c]				
married	27	44.3	5	38.5
never married	24	39.3	6	46.2
divorced	9	14.8	2	15.4
widowed	1	1.6		
Educational[d]				
elementary school	18	29.5	8	61.5
high school	30	49.2	5	38.5
higher	13	21.3		
Treatment medication[e]				
fluvoxamine	31	50.8	5	38.5
imipramine	30	49.2	8	61.5
Treatment completers[f]				
completers	61	100	2	15.4
dropouts			11	84.6
MDCL diagnosis[g]				
Mood disorder (M)	15	24.6	2	15.4
Anxiety disorder (A)	27	44.3	9	69.2
Comorbid M-A	19	31.1	2	15.4
CIDI diagnosis[h]				
Mood disorder (M)	14	23		
Anxiety disorder (A)	12	19.7	2	50.0
Comorbid M-A	32	52.5	2	50.0
No diagnosis	3	4.9		

Note. [a] $t = -1.55$, $p > .05$; [b] $\chi^2(1,74) = .34$, $p > .05$; [c] $\chi^2(3,74) = .42$, $p > .05$; [d] $\chi^2(2,74) = 6.16$, $p < .05$; [e] $\chi^2(1,74) = .65$, $p > .05$; [f] $\chi^2(1,74) = 60.63$, $p < .001$; [g] $\chi^2(2,74) = 2.71$, $p > .05$; [h] $\chi^2(3,65) = 2.72$, $p > .05$

5 A comparison of clinical diagnosis and diagnosis based on the Composite International Diagnostic Interview: comorbidity and agreement in diagnosing mood and anxiety disorders

Summary

In the present study diagnoses based on clinical judgement are compared to diagnoses based on a structured diagnostic interview for 96 patients with mood and anxiety disorders. The Munich Diagnostic Checklists (MDCL) were used by psychiatrists to arrive at DSM-III-R diagnoses. The psychologists undertook the Composite International Diagnostic Interview (CIDI) to also arrive at DSM-III-R diagnoses. The diagnostic agreement between the psychiatric diagnosis using the MDCL and the CIDI diagnosis was found to be moderate for major depression (k = .47). Fair agreement was found for social phobia (k = .40), panic disorder with and without agoraphobia (respectively k = .36 and k = .29), bulimia nervosa (k = .32) and dysthymia (k = .26). Poor agreement was found for generalized anxiety disorder and agoraphobia without panic attacks. According to the CIDI, comorbid mood and anxiety disorder existed in 49% of the patients while the psychiatrists found comorbidity in only 25% of the patients. The data suggest that psychiatrists choose between mood and anxiety disorder while the CIDI find both diagnoses. This suggests that comorbidity may not be the focus of attention for many clinicians. The only moderate agreement is not in line with other studies in which the agreement was found to be satisfactory. The present study casts doubt on the validity of the diagnostic procedures used, while previous studies appear to confirm the reliability of the diagnostic instruments.This poses a problem for the interpretation and generalisation of outcome studies on both the psychological and pharmacological treatments of mood and anxiety disorders.

Introduction

One of the problems in diagnosing mood and anxiety disorders is the comorbidity of mood and anxiety disorders or, put differently, the overlap of symptoms related to depression and anxiety. This problem is apparent in the changes that have occurred in the criteria for mood and anxiety disorders in the succeeding editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 1980, 1990, 1994). The problem is also evident in the 10th revision of the International Classification of Diseases (ICD-10) (WHO, 1990a) where 'mixed anxiety depression' is recognised as a separate category. In our research into the efficacy of antidepressants across different mood

and anxiety disorders, the reliability and validity of the diagnosis is a major issue. In a recent study we therefore included two diagnostic procedures for comparison: Clinical diagnosis by the treating psychiatrists (as usual in most trials of antidepressants) and diagnosis based on a structured interview (as usual in many epidemiological studies). The results of our comparison are reported here.

In an attempt to stimulate a more systematic diagnostic process the Munich Diagnostic Checklists (MDCL) have been developed. The MDCL contain checklists for each of the most important and frequently occurring psychiatric diagnoses based on the systems DSM-III-R and/or ICD-10 classification systems (Hiller, Zaudig, & Mombour, 1990a, 1990b). Thirty separate lists are involved, and each checklist represents a single diagnostic category. Each checklist contains all of the criteria needed for a complete evaluation of the corresponding disorder and a diagnostic decision, although the manner in which a particular item is assessed is left completely up to the clinician. The reliability of diagnoses based on the checklists has been found to be satisfactory (Hiller, Von Bose, Dichtl, & Agerer, 1990c). High agreement between raters has been obtained for major depression (k = .73) and bipolar disorder (k = .85). Furthermore, a high level of agreement has been obtained in an overall analysis for anxiety disorders (k = .76). Less agreement has been found for agoraphobia, social phobia and dysthymia which may be due to flaws in their definition and/or operationalisation. However, Hiller et al. have suggested that diagnostic disagreement may also indirectly arise from the DSM-III-R concept of comorbidity.

The Composite International Diagnostic Interview (CIDI) (WHO, 1990b) is a completely structured interview which combines questions from the Diagnostic Interview Schedule (DIS) with questions designed to elicit Present State Examination (PSE) items (Robins et al., 1988). The CIDI assesses mental disorders using the criteria from the tenth revised version of the International Classification of Diseases (ICD-10, Diagnostic Criteria for Research) and the third revised version of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-III-R) (Essau & Wittchen, 1993). The CIDI was designed for use in epidemiological studies with normal populations, is available in a variety of languages and cultures, and is currently being used for clinical and other research purposes as well (Wittchen, 1994). In a review of the reliability and validity of the CIDI, Wittchen (1994) reports good to excellent test-retest and interrater reliability for most diagnoses. Use of the CIDI is thus judged to be acceptable for different subjects in different settings and different countries. Only a few aspects of the validity of the CIDI have been examined to date and mostly in smaller, select clinical samples.

In a study on a comparison of the CIDI with clinical DSM-III-R criteria checklist diagnoses, the overall diagnostic concordance was found to be good (k = .78) (Janca, Robins, Bucholz, Early, & Shayka, 1992). To our

knowledge, this is the only comparison study using the CIDI. The sample consisted of 32 primary care, psychiatric outpatient or volunteer subjects. In 16 cases, the psychiatrist was an observer during the CIDI interview and coded his or her clinical impressions using the DSM-III-R checklists. Clearly, further studies on the validity of the CIDI with clinical instruments are needed (Wittchen, 1994).

Methods

Participants

A total of 108 patients newly attending three ambulatory mental health services in The Netherlands who were screened at intake by a psychiatrist, fulfilled DSM-III-R criteria of a mood or anxiety disorder and showed at least 'moderate' severity of their illness on the Clinical Global Impression (Guy, 1976). The patients were between 18 and 65 years of age. After inclusion, a comprehensive structured interview to assess DSM-III-R diagnoses again was conducted in 96 of the selected patients: 60 females and 36 males with a mean age of 36 years (ranging from 18 to 64, $SD = 10.92$).

Diagnostic assessments

The *Munich Diagnostic Checklists (MDCL)* were used by the psychiatrist to make a diagnosis in accordance with the DSM-III-R (Hiller et al., 1990a, 1990b). To encourage adoption of a more systematic diagnostic procedure, the use of the MDCL was semistructured by selecting a subset of the 30 checklists which had to be completed all. For the present study, a subset of 14 checklists was used: adjustment disorder, agoraphobia, alcohol dependence and abuse, bulimia nervosa, cyclothymia, dysthymia, generalized anxiety disorder, major depressive disorder, obsessive compulsive disorder, panic disorder with and without agoraphobia, schizoaffective disorder, simple phobia, social phobia and somatization disorder. The checklists were administered by the treating psychiatrist as part of the routine screening prior to the initiation of treatment. A total of four psychiatrists participated in the study.

The *CIDI* (WHO, 1990b) was administered by an independent psychologist trained at the Dutch WHO-CIDI Centre. A total of four psychologists participated in our study. The CIDI was administered four weeks after the start of treatment and took about 90 minutes to complete.

Statistical analysis

The kappa statistic (Cohen, 1960) was calculated as a measure of the association between the psychiatrist's diagnosis based on the MDCL and the psychologist's diagnosis based on the CIDI. The interpretation of the k coefficient was based on the rules laid down by Landis and Koch (1977): <.00 'poor'; .00-.20 'slight'; .21-.40 'fair'; .41-.60 'moderate'; .61-.80 'substan-

tial'; and .81-.1.00 'almost perfect'. Although the kappa statistic is known to decrease dramatically under low base rate conditions (Spitznagel & Helzer, 1985), it is currently the standard method used to assess diagnostic concordance in the field of psychiatry. Careful interpretation of the kappa statistic in connection with low frequency is thus called for. We also assessed the degree of concordance at a broader level by comparing diagnoses involving mood, anxiety and comorbid mood-anxiety disorders. These composite diagnostic categories consisted of 1) major depressive disorder and dysthymia (mood disorder), 2) panic disorder with and without agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, social phobia, simple phobia and agoraphobia without history of panic disorder (anxiety disorder) and 3) the comorbid mood-anxiety group with diagnoses of both mood and anxiety disorder.

The MDCL diagnoses were scored positively when coded with 'met' but not when coded with 'probably met'.

Results

In 96 patients MDCL-based diagnoses and CIDI-based diagnoses were available. The MDCL-based diagnoses were made by the psychiatrist at screening, whereas the CIDI-based diagnosed were assessed after inclusion only for the selected patients. Then agreement between the clinical diagnosis and CIDI-based diagnosis was studied for the selected group of patients with mood or anxiety disorders.

The psychiatrists produced a total of 177 MDCL-based diagnoses for the 96 patients, which is a mean of 1.84 diagnoses per patient. The psychologists produced a total of 248 CIDI-based diagnoses, which is a mean of 2.58 diagnoses. Three patients did not meet the full criteria for any current DSM-III-R diagnosis using the CIDI. The total number of diagnoses per patient was also found to differ for the CIDI and the MDCL. According to the MDCL, 48 patients (50%) had a single diagnosis and an additional 26 patients (27%) had two diagnoses. According to the CIDI, only 27 patients (28%) had a single diagnosis, 21 patients (22%) had two diagnoses, and another 21 patients (22%) had three diagnoses. Some 24 patients (25%) had four to six diagnoses according to the CIDI while the psychiatrist produced four or more diagnoses using the MDCL in only 7 patients (7%).

Using both the CIDI and the MDCL, major depression was most commonly diagnosed followed by panic disorder with agoraphobia, as can be seen in Table 5.1.

Furthermore, dysthymia, social phobia, simple phobia and generalized anxiety disorder were diagnosed frequently. Low frequencies were found for bulimia nervosa, obsessive compulsive disorder and agoraphobia without panic disorder, which indicates that careful interpretation of the kappa statistic

is needed for these categories. In addition to the mood and anxiety disorders, additional diagnoses were made using the CIDI for 15 patients: four patients were diagnosed with alcohol dependence, three patients with alcohol abuse, seven patients with somatoform pain and one patient with a schizophrenic disorder.
Relative to the diagnoses based on the MDCL, simple phobia and social phobia were diagnosed more frequently using the CIDI. Conversely, generalized anxiety disorder was diagnosed more often using the MDCL (23 times) than the CIDI (seven times).

Table 5.1 *DSM-III-R diagnoses based on MDCL and CIDI (n=96)*

DSM-III-R diagnosis	MDCL n	CIDI n
Major depression	45	63
Dysthymia	14	22
Panic disorder	3[a]	
with agoraphobia	30	41
without agoraphobia	14	8
Simple phobia	18	32
Social phobia	16	36
Generalized anxiety disorder	23	7
Agoraphobia without panic disorder	6	10
Obsessive compulsive disorder	7	9
Bulimia nervosa	1	5
Alcohol dependence		4
Alcohol abuse		3
Somatoform pain		7
Schizophrenic disorder		1
Total	177	248

Note. [a] Specification with/without agoraphobia unknown.

Examination of Table 5.2 shows that concordance between the CIDI and MDCL is moderate for the diagnoses of major depression (k = .47) and obsessive compulsive disorder (k = .46). Fair agreement was found for: social phobia (k = .40), panic disorder with and without agoraphobia (k = .36 and k = .29, respectively), bulimia nervosa (k = .32) and dysthymia (k = .26). The diagnoses for generalized anxiety disorder and agoraphobia showed kappa's around zero. The kappa's for obsessive compulsive disorder, buli-

mia nervosa and agoraphobia should nevertheless be interpreted with caution due to their low frequency. Disagreement was strongest for the diagnosis of generalized anxiety disorder. This diagnosis was made for 7 patients using the CIDI and 23 patients using the MDCL, with only one of the patients diagnosed similarly by the two instruments.

Table 5.2 *Diagnostic agreement between MDCL and CIDI diagnoses (n=96)*

DSM-III-R diagnosis	**CIDI**	**MDCL** +	-[a]	*k*
	+	a	b	
	-	c	d	
Major Depression		41	22	.47*
		4	29	
Obsessive		4	5	.46*
Compulsive disorder		3	84	
Social Phobia		14	22	.40*
		2	58	
Panic disorder with		21	20	.36*
agoraphobia		9	46	
Bulimia nervosa		1	4	.32*
			91	
Panic disorder without		4	4	.29*
agoraphobia		10	78	
Dysthymia		7	15	.26*
		7	67	
Simple Phobia		8	24	.11
		10	54	
Generalized Anxiety		1	6	-.05
disorder		22	67	
Agoraphobia without			10	-.09
panic disorder		6	80	

Note. [a] + = diagnosis present, - = diagnosis absent. * *k* value significant at 1% level.

Comorbidity of mood and anxiety disorders

According to the CIDI, mood and anxiety disorders existed comorbidly in 49% of the patients, as shown in Table 5.3. Some 26% of the patients had a pure anxiety disorder, 22% had a pure mood disorder and 3% had no DSM diagnosis according to the CIDI. The MDCL showed a different pattern: 51% of the patients were diagnosed as having an anxiety disorder without comorbid mood, 24% were diagnosed as having solely a mood disorder and 25% were diagnosed with comorbid mood and anxiety disorders.

Table 5.3 *Agreement between MDCL and CIDI for anxiety disorders, mood disorders, and comorbid mood-anxiety disorders*

	MDCL			
	Anxiety	Mood	Comorbid MA[a]	total
CIDI	n	n	n	n
Anxiety	23	-	2	25 (26%)
Mood	3	15	3	21 (22%)
Comorbid MA[a]	18	10	19	47 (49%)
No diagnosis	3	-	-	3 (3%)
Total	47 (49%)	25 (26%)	24 (25%)	96 (100%)

Note. [a] Comorbid mood and anxiety disorder.

k value = .43, $p < .001$ (n=93).

For the three composite diagnostic categories, the agreement between the CIDI and the MDCL was found to be moderate. Disagreement was mainly due to the fact that 28 patients were diagnosed with a comorbid mood and anxiety disorder using the CIDI, whereas a pure anxiety disorder or a pure mood disorder was diagnosed using the MDCL. Conversely, 5 patients were diagnosed with a comorbid mood and anxiety disorder according to the MDCL but not according to the CIDI. Total disagreement was found for three patients who were diagnosed with a mood disorder according to the CIDI and an anxiety disorder according to the MDCL. No diagnosis could be made for 3 patients using the CIDI. This was not restricted to DSM diagnoses of mood or anxiety disorders. Based on the 93 patients with a diagnosis, the overall concordance between the CIDI- and MDCL-based diagnoses of the anxiety disorders, mood disorders or comorbid mood-anxiety group was found to be moderate (k = .43).

Discussion

The present study shows only moderate agreement between the clinical diagnoses of mood disorders, anxiety disorders, and comorbid mood-anxiety disorders by psychiatrists (using the MDCL) and the diagnoses using the CIDI. Disagreement was mainly due to the diagnosis of comorbid mood and anxiety disorders using the CIDI and either anxiety disorder alone or mood disorder alone using the MDCL. Of the DSM-III-R categories, the diagnosis of major depression showed the greatest degree of agreement although no more than moderate agreement. Social phobia and panic disorder both with and without agoraphobia showed only fair agreement, and poor agreement was found for generalized anxiety disorder. All patients were screened on either a mood or anxiety disorder and after this preselection agreement on diagnosis between two diagnostic procedures were examined. Taken into consideration that agreement was assessed within this selected patientgroup, no more than moderate agreement is of concern.

This overall lack of agreement is in contrast with other comparison studies in which the concordance between differently derived diagnoses has been found to be satisfactory (Janca et al., 1992; Kovess Sylla, Fournier, & Flavigny, 1992). However, the other studies were focused on the validation of diagnostic instruments by comparison to actual clinical diagnosis. In the study by Janca et al. (1992), for example, the clinical diagnosis was made by the psychiatrist during observation of the CIDI interview. Such a procedure is quite uncommon clinical practice and may remove most of the variance due to differences in interview style and information, with a higher level of agreement between the diagnoses as a result. In the present study, the focus was on the agreement between the psychiatrists' diagnoses using the MDCL and the diagnoses using the standardised CIDI interview, independent of each other. We showed agreement to be low when two independent procedures are used, which has important implications for the validity of psychiatric diagnoses.

An example of the validity problem is as follows. In most treatment outcome studies with antidepressants, the DSM categories are used for inclusion but then according to the psychiatrists and without the use of such a structured list as the MDCL or only with a list of the diagnoses relevant to the study. In other words, the population included in the study may differ depending on the procedures used by the psychiatrists and the focus of the research. Which of the two procedures, the MDCL or the CIDI, is suited best for measurement of the DSM categories remains unclear due to the lack of a 'golden standard' for psychiatric diagnosis (Faraone & Tsuang, 1994). Clinical diagnosis is often used as the standard, but this is neither careful nor valid. And due to the lack of a golden standard, the differentiation between anxiety and mood remains a problem along with the validity of diagnosis of mood and anxiety disorders.

The comorbidity of mood and anxiety disorders was found to be high according to the CIDI. The psychiatrists using the MDCL diagnosed both disorders simultaneously less frequently compared to the CIDI diagnoses. In daily practice, clinicians may actually tend to choose between mood and anxiety disorder as this is implicit in the DSM decision trees (APA, DSM-IV: pp. 696-699; DSM-III-R: pp. 380-385; DSM-III: pp. 342-344). There is also a diagnostic tradition of making single diagnoses rather than more diagnoses. In clinical trials for the treatment of anxiety disorders, patients with concurrent major depression are often excluded, for example. And our results show that a nonexclusive (i.e., comorbid) diagnosis may not even occur if the clinical diagnosis of the psychiatrist is used. We must emphasise that the paucity of comorbid diagnoses was produced by the psychiatrists even though they completed the MDCL for all of the mood and anxiety disorders. Thus, the psychiatrists did not miss comorbid diagnoses only because they did not consider them.

The inclusion of the patients in a clinical trial solely on the basis of a psychiatric diagnosis can certainly complicate the interpretation of the results. The unclear validity of the psychiatric diagnosis may also explain certain contradictory results, as discussed by Ansseau (1992), who showed trials from Europe and the United States to often be contradictory due to differences in clinical material, methodologies, health service systems, psychiatric traditions and the types of patients used on the two continents. The value of treatment outcome studies for clinical practice is, of course, based on the accuracy of the diagnosis. The use of such diagnostic checklists as the MDCL may help diminish this lack of consensus but continue to be rarely used in clinical research, unfortunately.

The current study also has some limitations to consider. The diagnostic instruments selected for comparison were assumed to measure the same construct, namely diagnoses according to the DSM-III-R criteria. Some degree of disagreement could be expected as a result of the fundamental differences in the procedures and differences in the amount of time devoted to assess diagnosis. The CIDI, for example, is a fully structured instrument and strictly measures all available diagnoses in terms of the criteria formulated within the DSM. No interpretations on the part of the interviewer is needed or allowed. The MDCL, in contrast, is just a helping hand for the clinician, who relies on his or her own questions, observations and other information to decide which checklists to complete (Wittchen & Essau, 1993). To encourage adoption of a more systematic diagnostic procedure in the present study, we semistructured the use of the MDCL by selecting fourteen of the thirty checklists which had to be completed all. Nevertheless, comorbid patterns of symptoms were still interpreted as part of one or the other disorder and not as a comorbid disorder, depending on the clinicians observation and interpretation.

The concordance between the psychiatric diagnosis using the MDCL and the diagnosis using the CIDI may also have been reduced by assessment at different points in time. The psychiatrist made the diagnosis during the screening phase, while the CIDI was conducted four weeks after the start of treatment. As the CIDI is designed to examine symptoms of the last episode retrospectively, however, comparison of the CIDI with the MDCL seems to be justified.

In conclusion, the present study shows important differences in the diagnosis of mood and anxiety disorders when different diagnostic procedures are followed. Such inconsistency poses not only a problem for the interpretation of research results but also for the generalisation of outcome studies with regard to both psychological and pharmacological treatments.

Note. Submitted for publication

6 Diagnosis at first episode to differentiate antidepressant treatment response in patients with mood and anxiety disorders

Summary

Comorbidity of mood and anxiety disorders is often ignored in pharmacotreatment outcome studies, which complicates the interpretation of treatment response. The clinical trials are usually based on single DSM categories. The present study is a first attempt to differentiate response to antidepressants with a design which differs from that used in previous clinical trials. To avoid bias due to comorbidity, we included patients with any DSM-III-R diagnosis of mood or anxiety disorder for which antidepressant treatment was indicated. We also explored the role of the diagnosis at first episode in the efficacy of the different antidepressants. A total of 92 outpatients with a mood and/or anxiety disorder were randomly assigned to treatment with imipramine or fluvoxamine in a 6-week study. The diagnosis at first episode, or primary diagnosis, was available for 78 patients, 40 with a primary depression and 38 with a primary anxiety disorder. Analyses using the MIXED procedure for repeated measures showed no general differences between treatment with imipramine versus fluvoxamine. When the primary diagnoses were taken into consideration, differentiation occurred. Patients with primary depression showed better response to imipramine than to fluvoxamine at 2 weeks, but not at 6 weeks of treatment. The assumption that patients with primary anxiety disorder would respond better to fluvoxamine than to imipramine was observed for only the CGI, and not the CPRS-MA. Given the exploratory nature of the study, however, replication of our finding is needed. Further study of the role of primary diagnosis is also needed, along with further validation of the outcome measures.

Introduction

Tricyclic Antidepressants (TCAs) as well as Selective Serotonin Reuptake Inhibitors (SSRIs) are effective for the treatment of depression (Song et al., 1993) and such anxiety disorders as panic disorder, obsessive compulsive disorder, social phobia and generalized anxiety disorder (Black, Wesner, Bowers, & Gabel, 1993; Burke, Preskorn, Bloom, & Kupfer, 1995; Kent, Coplan, Gorman, 1998; McTavish & Benfield, 1990; Murphy & Pigott, 1990; Rickels, Downing, Schweizer, & Hassman, 1993; Rocca, Fonzo, Scotta, Zanalda, & Ravizza, 1997; Tancer & Uhde, 1995; Van Balkom, 1994; Van Balkom et al., 1997; Wilkinson, Balestrieri, Ruggeri, & Bellantuono, 1991). Some studies suggest that TCAs may be more effective for certain types of

depression (Klein & Ross 1993; Kraghsorensen, 1990; Potter, Rudorfer, & Manji, 1991) and SSRIs may be more effective for certain anxiety disorders (DenBoer & Westenberg, 1988; Van Balkom, 1997). It has also been suggested that SSRIs may be particularly effective for atypical depression (Pande et al., 1996). Most studies do not find such differences, however, which has resulted in the opinion that TCAs and SSRIs are equally effective for depression (Andrews & Nemeroff, 1994). Although SSRIs are allegedly preferred for the treatment of anxiety disorders because of the contention that they act more specifically on the disturbed serotonergic system, their relatively benign side effects are actually the reason for such a preference in clinical practice(Kent et al., 1998).

Clinical trials always include patients meeting the DSM criteria for a single specific disorder, which obviously ignores comorbidity, even though this tends to be the rule with such disorders. It is also therefore not clear whether the paucity of results differentiating TCAs and SSRIs, is related to this artificial separation of categories of illnesses.

The preceding lack of differentiation between response to TCAs and SSRIs may also be related to the DSM categories being based on mainly the current symptomatology and not the development of the syndrome. It has been suggested, for example, that depression may be 'primary' (Cloninger et al., 1990) or 'pure' (Winokur, 1997), on the one hand, or secondary to anxiety disorders or an emotionally unstable personality, on the other hand.

The present study is a first attempt to differentiate response to antidepressants using a different design than in from previous clinical trials. First, we included patients with any DSM-III-R diagnosis of mood or anxiety disorder for which antidepressants were indicated and sufficient severity occurred to warrant treatment. Our aim was to avoid the bias associated with the selection of specific DSM categories and to explore the possibility of treatment differences when syndrome or symptomatic extremes for these disorders are included in a single study. We also explored the role of the first episode and the assumption that patients with a first depressive episode ('primary depression') would respond better to treatment with a TCA and patients with a first anxiety episode ('primary anxiety disorder') would respond better to treatment with an SSRI.

Methods

Design

Patients with either a mood or anxiety disorder according to the DSM-III-R were randomly treated with either imipramine or fluvoxamine for six weeks. To include a representative outpatient sample and avoid selection bias, the treatment was not blind to the treating psychiatrists, but the crucial ratings were performed by a blind rater.

Subjects

All newly attending patients at a community mental health centre in The Netherlands between 18 and 65 years of age were screened for anxiety or mood disorders using the DSM-III-R criteria. Those patients with at least a moderate (4) illness severity on the Clinical Global Impression (CGI: Guy, 1976) were included. The following exclusion criteria were applied: a) contra indications for antidepressant drugs, b) unsuccessful treatment with fluvoxamine or imipramine during the present episode, c) treatment with another antidepressant less than one week prior to randomisation and fluoxetine less than five weeks prior to entering the study, d) concurrent use of CNS medication other than for night time sedation and/or to control anxiety, and e) use of psychedelics or daily use of alcohol (consisting of more than 3 drinks a day for the latter).

During most of the study period, we collected intake data on the entire population at the clinical site to gain greater insight into the selection procedures. In this period, 1235 patients were seen for intake and 564 (45.7%) were diagnosed with a mood or anxiety disorder based on the DSM classification; 31.4% with an anxiety disorder, 23.2% with a major depressive disorder, 21.1% with an adaptation disorder, 12.8% with dysthymia, 7.6% with post traumatic stress disorder, 2.5% with obsessive compulsive disorder and 1.4% with a bipolar disorder. Eighty-four (14.9%) of these 564 patients were included in the current study. The main reason for not including patients was insufficient severity (CGI below 4, 249/564 patients, 44.1%). This resulted in the exclusion of all patients with an adaptation disorder and most of the patients with dysthymia, obsessive compulsive disorder, post traumatic stress disorder and social and simple phobia. Additional reasons for exclusion were: current use of other antidepressants (5.4%), crisis intervention (2.5%), hospitalisation (1.6%), severe alcohol or drug abuse (1.6%), lack of Dutch language capabilities (2.3%), refusal of medical treatment (3.4%), refusal to cooperate in the treatment study (1.0%) and other (1.7%). The reason for exclusion remained unknown for 19.7% of the patients. A total of 98 patients thus entered the study, and 92 patients actually started treatment. After randomisation and before initiation of treatment, five patients refused to participate further and one patient turned out to meet one of the exclusion criteria.

Treatment conditions

The patients were randomly treated with either imipramine or fluvoxamine. The dosage of fluvoxamine was 50 mg on the first day and increased to 150 mg/d at the end of the first week. A temporary decrease of the dosage due to side effects was allowed, but the dosage of 150 mg/d had to be reached within 14 days of the first treatment day. During week 2 through 6, a minimum dosage of 150 mg/d was maintained. During week 4 through 6, the dosage could be increased to a maximum of 200 mg/d in cases of non-response. The

imipramine was started at 75 mg/d. After one week, blood was collected for blood level determination and assessed within five days. The dosage of imipramine was then adjusted to obtain blood levels of 200-300µg/1 of the sum of imipramine and desmethylimipramine, which was checked at week 4.

Diagnostic Assessments

The Munich Diagnostic Checklists (MDCL) were used by the treating psychiatrists to screen for the DSM-III-R criteria (Hiller et al., 1990a, 1990b). A subset of the MDCL checklists was used: those checklists pertaining to adjustment disorder, agoraphobia, alcohol dependence and abuse, bulimia nervosa, dysthymia, generalized anxiety disorder, major depressive disorder, obsessive compulsive disorder, panic disorder, schizo affective disorder, simple phobia, social phobia and somatization disorder. The full subset was completed for all patients and issues of hierarchy were disregarded.

The Clinical Global Impression severity measure (CGI) (Guy, 1976) was completed by the psychiatrist and had to be at least 4 (i.e., moderate) for the patient to enter the study.

The Dutch version 1.1 (Smeets & Van den Ham, 1994) of the Composite International Diagnostic Interview (CIDI) (WHO, 1990) was administered four weeks after initiation of treatment by a trained research psychologist blind to all aspects of the treatment. The CIDI was used to obtain the diagnosis of the first episode, needed to distinguish between primary and secondary diagnosis based on sequential relationship of diagnoses. All patients with a major depression or dysthymia according to the DSM-III-R as their first illness episode were classified as having a primary depression, whether with or without a comorbid anxiety disorder. It is assumed that patients diagnosed with a comorbid mood and anxiety disorder at the first episode, experienced mixed mood and anxiety symptoms that would be part of one underlying mood disorder. All patients with an anxiety disorder without a comorbid mood disorder according to the DSM-III-R as their first episode were classified as having a primary anxiety disorder.

Outcome Measures

To assess response to treatment, an instrument suitable for the quantification of anxiety as well as depressive symptoms was needed. For this purpose, a composite of the subscales from the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al., 1978) for depression (MADRS) (Montgomery & Åsberg 1979), anxiety (BSA) (Tyrer et al., 1984) and the OCD (Montgomery & Montgomery, 1980; Thorén et al., 1980) was used. This composite scale, the 'mood and anxiety subscale' of the CPRS (CPRS-MA) consists of 21 items (18 symptoms and 3 observed items). The CPRS-MA is similar to the recently developed self-rating scale for depression and anxiety states (CPRS-S-A) from the original CPRS (Svanvorg & Åsberg, 1994) which consists of 19 items. Seventeen items are the same as in the CPRS-

MA with the item 'inner tension' from the CPRS-MA split into 'inner tension' and 'panic attacks' in the CPRS-S-A. Obviously, the 3 observed items were not included in the self rating scale. The CPRS-MA was completed by the research psychologist. The CGI-severity measure was completed by the research psychologist being a general outcome measure showing good sensitivity to change in clinical trials (Leon et al., 1993).

Procedure

The patients visited the psychiatrist weekly for the first two weeks and then every two weeks. The visits took an average of about 20 minutes. On each visit, the patients were asked whether they had experienced any physical or other health problems; no side effects were suggested. No additional psychotherapy was provided. The research psychologist administered the CPRS and CGI the day the patient started with the medication (baseline), at two weeks of treatment (week 2) and at six weeks of treatment (week 6).

No concomitant medication was allowed, with the exception of oxazepam or lormetazepam during the first 4 weeks. During weeks 4 through 6, these benzodiazepines were not allowed. In fact 45 patients (49%) (24 imipramine, 21 fluvoxamine) were prescribed oxazepam (mean dose 21.8 mg/d; range 5 to 50); 11 patients (5 imipramine, 6 fluvoxamine) were prescribed lormetazepam (9 received the maximum dose of 2 mg/d); and 10 patients (4 imipramine, 6 fluvoxamine) were prescribed both medications. Two patients were prescribed other concomitant medications (alprazolam, diazepam) and 7 patients were prescribed concomitant medication during weeks 4 through 6 (2 oxazepam, 3 lormetazepam, 2 combination).

Statistical analysis

The data were entered into a relational database, processed using DMSS (Broekman, 1994) and transferred to SAS\STAT software release 6.12 (SAS, 1997). The data were analysed using the MIXED procedure for repeated measures. Five measurements were excluded, three at week 2 and two at week 6, because they deviated more than seven days from week 2 or more than 14 days from week 6.

To test the efficacy of the different treatments a univariate mixed procedure for repeated measures was used (SAS, 1997) with the CPRS-MA as the main outcome measure. The CGI data were also analysed in a similar manner. The model consisted of the between-subjects factor Treatment group (imipramine/fluvoxamine) and the within-subjects factor Assessment (baseline/ week 2/week 6) and their two-way interaction. To test for diagnostic differences related to treatment response, the same procedure was used with the diagnosis at first episode (Primary depression/Primary anxiety) also entered into the model. The two- and three-way interactions of Treatment group, Assessment and Primary diagnosis were included.

To specify at what point in time differentiation may have occurred, we entered two contrast statements into the model, namely the contrast between baseline and week 2, and the contrast between baseline and week 6. Finally, we tested the contrast statements for the groups of patients with primary depression and primary anxiety disorder separately as well.

An advantage of the mixed procedure for repeated measures above analyses of variance procedures is that missing values, basically due to drop-outs, do not lead to data reduction (Everitt, 1998). All intent-to-treat (ITT) cases were included in the analyses, independent of missing data at week 2 or week 6, which makes the mixed procedure preferable over such alternatives as LOCF analyses (L(ast) O(bservation) C(arried) F(orward)) or Observed Cases analyses.

Results

Of the 92 patients who started treatment, 59 were female with a mean age of 34.5 (range 18-65, *SD* = 9.93). Forty-four patients received imipramine and 48 patients received fluvoxamine. Based on the diagnosis of the psychiatrist, 20 patients were included with a DSM-III-R major depressive disorder or dysthymia (22%), 46 patients with an anxiety disorder (50%) and 26 patients with both a mood and an anxiety disorder (28%). Forty patients were married, 38 patients were never married, 13 patients were divorced and one patient was a widow; 25 patients lived alone, 29 patients lived with a partner and 38 patients lived with their family. With regard to educational level: 9% had finished elementary school, 76% had finished high school and 15% had finished some form of higher education.

The six weeks of treatment were completed by 77 patients (81%), 35 on imipramine and 42 on fluvoxamine. Nine of the imipramine patients dropped out and 6 of the fluvoxamine patients; 11 of the 15 dropouts were within the first two weeks of treatment. For 5 of these patients the psychiatrist decided to stop treatment due to unacceptable side effects of the study medication. The other 10 dropouts (71%) decided themselves to stop treatment for the following reasons: unacceptable side effects (1: on fluvoxamine), non-compliance with treatment (4: 3 on imipramine and 1 on fluvoxamine), non-compliance with the study procedures (4: 2 on imipramine and 2 on fluvoxamine) and lack of effect (1: on fluvoxamine).

For the total sample of patients with mood and/or anxiety disorders (n = 92), no significant differences between treatment with imipramine versus fluvoxamine were found. That is, no main effect of Treatment group ($F(2, 90) = 2.34$, $p = .12$) and no interaction effect between Treatment group and Assessment ($F(2, 90) = 2.21$, $p = .11$).

Diagnosis at first episode and treatment efficacy

The CIDI interview to assess lifetime diagnosis was conducted with 81 of the 92 patients. Two patients did not meet the criteria for any DSM-III-R diagnosis, and one patient met only the criteria for a simple phobia according to the CIDI. Of the remaining 78 patients, 40 were identified as having a primary depression (20 on imipramine and 20 on fluvoxamine) and 38 as having a primary anxiety disorder (16 on imipramine and 22 on fluvoxamine).

The mean CPRS-MA score at baseline was observed to be higher for the group of patients with primary depression when compared to those with primary anxiety disorder although not statistically significant ($t = 1.34$, $p = .18$) (Table 6.1).

Table 6.1 *CPRS-MA and CGI Scores for Primary Diagnosis, Mean and Standard Deviation (n=78)*

	baseline			week2			week6		
	n	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*
Primary depression	40			39			39		
CPRS-MA									
imipramine	20	47.4	7.3	19	33.2	11.7	19	23.3	11.8
fluvoxamine	20	46.3	13.9	20	42.5	13.7	20	27.6	20.3
CGI-severity									
imipramine	20	4.70	0.47	19	4.21	0.63	19	3.37	0.90
fluvoxamine	20	4.85	0.49	20	4.70	0.57	20	3.55	1.23
Primary anxiety	38			36			35		
CPRS-MA									
imipramine	16	42.3	12.1	15	36.6	9.6	15	23.5	10.1
fluvoxamine	22	43.2	13.0	21	37.2	12.4	20	24.1	13.2
CGI-severity									
imipramine	16	4.88	0.62	15	4.80	0.41	15	4.00	0.65
fluvoxamine	22	4.86	0.56	20	4.50	0.76	19	3.32	0.89

The MIXED procedure analyses including primary diagnosis showed no main or interaction effects (Table 6.2).

Table 6.2 *MIXED Procedure for Repeated Measures with CPRS-MA (n=78)*

Tests of fixed effects				
Source	*NDF*	*DDF*	*TypeIII F*	*Pr > F*
Assessment (A)	2	74	77.77	.001 *
Treatmentgroup (T)	1	74	0.80	.373
Assessment*Treatment	2	74	1.87	.161
Primary diagnosis (P)	1	74	1.34	.250
Assess*Prim	2	74	0.43	.653
Treatment*Prim	2	74	0.33	.570
Assess*Prim*Treatment	2	74	2.01	.142
Contrast statements				
total interaction				
Baseline-week2	1	74	4.01	.049 *
Baseline-week6	1	74	0.48	.491
primary depression				
Baseline-week2	1	74	8.13	.006 *
primary anxiety				
Baseline-week2	1	74	0.00	.960

Note. $p < .05$

A significant difference was nevertheless observed for the effects of imipramine versus fluvoxamine between baseline and week 2 for primary depression as opposed to primary anxiety disorder (total interaction of Treatment group, Assessment and Primary diagnosis ($F(2, 74) = 4.01$, $p = .049$) but not between baseline and week 6 ($F(2, 74) = 0.48$, $p = .49$). We tested these interaction terms between baseline and week 2 for the primary diagnoses separately and found a significant Treatment group by Assessment interaction effect for primary depression ($F(2, 74) = 8.13$, $p = .0056$) but not for primary anxiety disorder ($F(2, 74) = 0.00$, $p = .96$). Based on the CPRS-MA, thus, imipramine showed a larger effect than fluvoxamine at 2 weeks of treatment in patients with primary depression but not at 6 weeks and not in patients with primary anxiety disorder (see Figure 6.1).

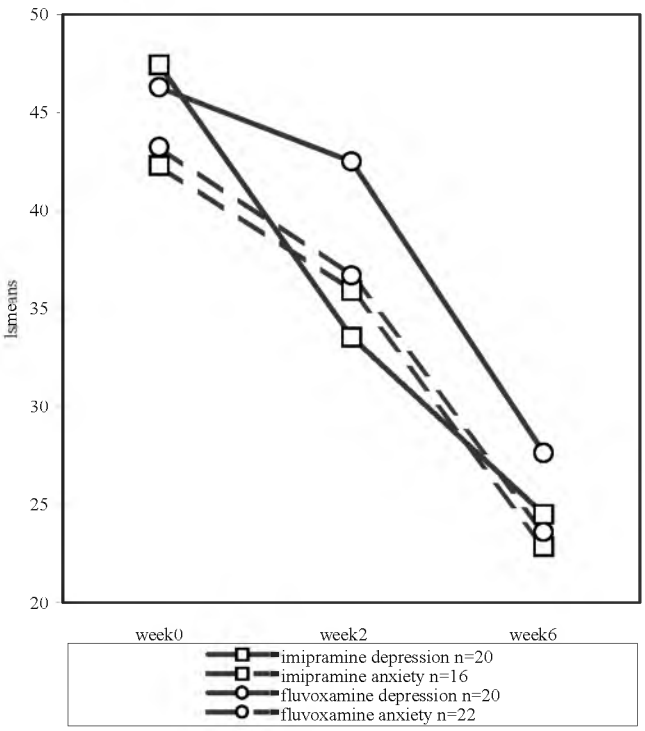


Figure 6.1 *CPRS-MA response of imipramine and fluvoxamine in primary depression and primary anxiety disorder*

The CGI results show a comparable pattern to those of the CPRS-MA for patients with primary depression (see Figure 6.2). In patients with primary anxiety disorders, moreover, treatment with fluvoxamine resulted in lower CGI scores at week 2 and week 6 than treatment with imipramine (interaction between Treatment group and Primary diagnosis: F (2, 74) = 5.19, p = .026; interaction between Treatment group, Primary diagnosis and Assessment F (2, 74) = 2.37, p = .10). The CGI scores thus show a better response to imipramine for primary depression and a better response to fluvoxamine for primary anxiety disorder.

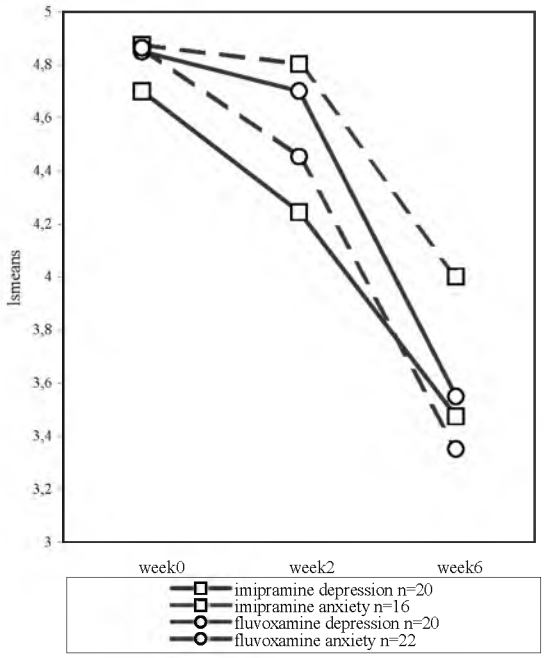


Figure 6.2 *CGI response of imipramine and fluvoxamine in primary depression and primary anxiety disorder*

It should be noted that 40 patients with a first depressive episode were allocated to the primary depression group, although 18 of these patients had a comorbid anxiety disorder, (i.e. the first episode met the criteria for a mood as well as anxiety disorder in 45% of the primary depression patients). We also compared the CPRS-MA results for the 22 patients with a first depressive episode without a comorbid anxiety disorder with the results for patients with a primary anxiety disorder (see Figure 6.3). The results were similar to those obtained for the primary depression group including comorbid anxiety disorders (significant interaction of Treatment group, Assessment and Primary diagnosis: F (2, 56) = 3.20, p = .048). However, the number of patients in these subgroups is restricted.

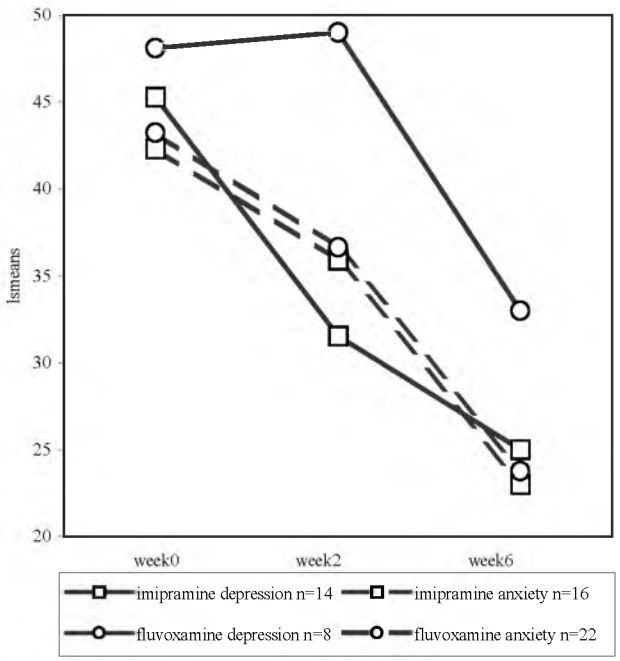


Figure 6.3 *CPRS-MA response of imipramine and fluvoxamine in primary depression without comorbid anxiety disorder and primary anxiety disorder*

In sum, patients with primary depression responded better to imipramine than to fluvoxamine at week 2 but not at week 6. The same was found for the subgroup of patients with primary depression without a comorbid anxiety disorder at first episode. Patients with primary anxiety disorder responded better to fluvoxamine than to imipramine at both week 2 and week 6 when assessed with the CGI, but not the CPRS-MA.

Discussion

The present clinical trial was a first attempt to differentiate response to antidepressants using a design different from that used in previous clinical trials. Patients with any DSM-III-R diagnosis of mood or anxiety disorder were included in the study. In such a manner, the artificial separation into DSM categories which are not in fact mutually exclusive is circumvented. As might be expected on the basis of the literature (Kessler et al., 1996), 28% of the patients indeed had a comorbid mood or anxiety disorder. Response to treatment with fluvoxamine versus imipramine was initially evaluated in this

group as an entity, i.e. across depressive and anxiety symptoms. For this purpose, we used a composite scale of the depression, anxiety and OCD items from the CPRS (CPRS-MA). Although similar to the CPRS-S-A (Svanvorg & Åsberg, 1994) the CPRS-MA has yet to be validated and we therefore used the CGI to also gain a general impression of the patient's improvement not explicitly relating to specific symptoms. For the patient group as a whole, no differences in the efficacy of treatment with fluvoxamine or imipramine were observed.

We further analysed differences in treatment response to fluvoxamine and imipramine by breaking down the patients according to the nature of their first illness episode. The CIDI was used to assess whether the first episode was a depression (primary depression) or an anxiety disorder (primary anxiety disorder). Support for the hypothesis that imipramine would be more effective for primary depression and fluvoxamine more effective for primary anxiety disorder was found. Patients with primary depression showed a better response to imipramine at week 2 (but not at week 6) according to both the CPRS-MA and the CGI. Patients with primary anxiety disorder, in contrast, showed a better response to fluvoxamine, according to CGI but not the CPRS-MA.

The origin of the differences in the results using the CPRS-MA and the CGI can only be guessed at. This may be related to psychometric qualities of the scales, including sensitivity and specificity, particularly in relation to the subgroups of patients studied here. The fact that the patients with primary depression have higher CPRS-MA scores at baseline than the patients with primary anxiety disorder hints at such an imbalance of items. Depressive symptoms appear to be emphasised more than anxiety symptoms within the CPRS-MA. The experience of panic attacks is subsumed under the item 'inner tension', which may make the instrument insufficiently sensitive to patients with primary anxiety disorder. The present results should therefore be interpreted as preliminary, and more research with the CPRS-MA should be undertaken in the future.

The CIDI was used to assess the diagnosis of the first illness episode in retrospect. Retrospective assessment always depends on the quality of a person's recall which cannot be assumed to be particularly high or of equal quality across the different patient categories (Andrews & Nemeroff, 1994). At this moment there seems to be no clear solution to this problem except for prospective studies. We are not aware of instruments superior to the CIDI at this moment.

It should be pointed out that, in contrast to most other trials, we used therapeutic drug monitoring (TDM) to determine the imipramine dosage. This circumvents the dosing problem in most other trials which may have led to overly aggressive dosages (resulting in high dropout rates) or to suboptimal dosages of imipramine (Burke et al., 1995). We have shown before

differences between imipramine and mirtazapine in depressed inpatients in a trial using TDM for imipramine (Bruijn et al., 1996).

In conclusion, despite the methodological problems yet to be solved the new paradigms used here to differentiate response to fluvoxamine, a SSRI, from response to imipramine, a TCA, appears to be promising. The results suggest that the nature of the first illness episode may be more valuable than the DSM categories of current mood or anxiety disorders, which may lend support to the concept of primary versus secondary depression (Cloninger et al., 1990) for purposes of differentiating treatment response.

Note. Submitted for publication

7 The role of temperament to differentiate antidepressant treatment response in patients with mood and anxiety disorders

Summary

Research on mood and anxiety disorders has not provided many clues with regard to differential response to pharmacological treatment. Temperament, according to the psychobiological personality model of Cloninger, appears to be promising for the differentiation of response to antidepressants. More specifically, the temperament dimension called Harm Avoidance is found to be consistently elevated in patients with mood and anxiety disorders. Responders and non-responders to antidepressant treatment have been distinguished according to their temperament scores, and non-responders found to score higher on Harm Avoidance than responders. In the present study, the role of temperament was explored to detect any differences in response to antidepressant treatment (with a TCA or SSRI) in 74 patients with mood or anxiety disorders.

The Tridimensional Personality Questionnaire (TPQ) was completed by 66 outpatients with a mood and/or anxiety disorder randomly assigned to treatment with either imipramine or fluvoxamine for six weeks. As expected, patients showed high scores on Harm Avoidance (61 completers, mean= 18.98; 5 dropouts, mean=20.00). Treatment response was evaluated using a subscale of the Comprehensive Psychopathological Rating Scale (CPRS-MA). Regression analysis based on the CPRS-MA for the 61 completers showed Harm Avoidance to be related to treatment response to antidepressants but not to treatment with imipramine versus fluvoxamine. There were no interaction effects between the temperament dimensions Harm Avoidance and Reward Dependence on treatment outcome. Furthermore, persistence was found to be related to treatment response in the fluvoxamine group. The influence of state mood effects on Harm Avoidance is discussed. Further research is needed to confirm the present findings and clarify the role of temperament in antidepressant treatment response, particularly in light of the new methods utilised in this study.

Introduction

The past decades have witnessed considerable progress in the treatment of mood and anxiety disorders with antidepressants. Tricyclic Antidepressants (TCAs) as well as Selective Serotonin Reuptake Inhibitors (SSRIs) have proved effective for the treatment of major depression (Anderson, 1998, 2000) and such anxiety disorders as panic disorder, obsessive- compulsive

disorder, social phobia and generalized anxiety disorder (Allgulander, 1999; Black, Wesner, Bowers, & Gabel, 1993; Burke, Preskorn, Bloom, & Kupfer, 1995; McTavish & Benfield, 1990; Murphy & Pigott, 1990; Rickels, Downing, Schweizer, & Hassman, 1993; Rocca, Fonzo, Scotta, Zanalda, & Ravizza, 1997; Stein, Fyer, Davidson, Pollack & Wiita, 1999; Tancer & Uhde, 1995, Van Balkom, 1994). Some studies suggest that TCAs may be more effective for certain types of depression (Klein & Ross, 1993; Potter, Rudolfer, & Manji, 1991) including depressed inpatients (Anderson, 2000; Kraghsorensen, 1990) and SSRIs may be more effective for certain anxiety disorders (Den Boer & Westenberg, 1988; Van Balkom, 1994). While the effectiveness of the latter is assumed to be connected to disturbed serotonergic neurotransmission in anxiety disorders (Kent, Coplan, & Gorman, 1998), it is still not possible to predict antidepressant treatment response for patients with mood and anxiety disorders or to meaningfully differentiate between the effects of TCAs and SSRIs.

The psychobiological personality model of Cloninger (Cloninger, 1987) is reputed to differentiate between responders and nonresponders to antidepressant treatment (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). Temperament dimensions refer to automatic emotional responses which are moderately heritable and stable throughout life. Large-scale twin studies have confirmed that the different dimensions of temperament are genetically homogeneous and independent of one another (Heath, Cloninger, & Martin, 1994; Stallings, Hewitt, Cloninger, Heath, & Eaves, 1996). The three dimensions of temperament considered in the model are Novelty Seeking, Harm Avoidance and Reward Dependence. The Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987) consists of 100 items rated using a self-rating scale. Novelty Seeking is a tendency towards intense excitement in response to novel stimuli, which leads to frequent exploratory activity or active avoidance of monotony and of potential punishment. Harm Avoidance is a tendency to respond intensely to signals of aversive stimuli and thereby a tendency to inhibit behaviour in order to avoid punishment, novelty and frustrative non-reward. Reward Dependence is a tendency to respond intensely to signals of reward and a related tendency to maintain behaviour and resist extinction of what has been previously associated with reward and/or relief from punishment (Cloninger, 1987). A subscale of Reward Dependence, called Persistence, has proved to be an independent dimension and represents the tendency to be hardworking, stable and industrious (Cloninger et al., 1994).

The temperament dimensions are postulated to reflect the underlying biogenetic structure of variations of the dopaminergic, serotonergic and noradrenergic brain system, which is moderately heritable and stable throughout life. Scores on Harm Avoidance have been found to be positively correlated with mesolimbic serotonergic activity (Cloninger et al., 1994). In addition, the temperament dimensions appear to be closely related to

susceptibility to different neurotic syndromes (Cloninger, Svrakic, & Przybeck, 1993). Cloninger concluded that depressives are clinically and etiologically heterogeneous and that temperament may be a more powerful manner of characterising their heterogeneity than their variation in depressive symptoms and any comorbid psychopathology.

Several studies have explored the role of temperament as a possible predictor of antidepressant response. Temperament has been found to be related to treatment response, although the results show limited consistency with regard to the role of the various dimensions or types (i.e., combinations) of temperament. Joffe et al. (1993) showed outpatients who were non-responders to standard antidepressant treatment for major depression to score higher on Harm Avoidance at both baseline and after three months of treatment when compared to outpatients who were responders. In addition, the Harm Avoidance scores of the non-responders remained relatively stable (mean scores of 26.8 and 26.7) while the Harm Avoidance scores of the responders changed over the course of treatment (mean scores of 21.9 and 18.2). In another study, specific combinations (or types) of temperament have been related to response to antidepressants (Joyce, Mulder, & Cloninger, 1994). In fact, type of temperament turned out to be the only predictor of treatment outcome when compared to personality disorder, severity of symptoms, age and gender. More recently, Nelson and Cloninger (1997) have shown patients with major depression and high scores on Reward Dependence to have the lowest antidepressant response. Harm Avoidance, Reward Dependence and their interaction clearly predicted treatment response. More specifically, patients with high scores on Harm Avoidance or Reward Dependence showed lower treatment response when compared to other patients. It should be noted that although the model appears to have significant predictive value due to the large number of patients included in the study, it actually accounts for only 1.1% of the variance in treatment response. Nelson and Cloninger therefore conclude that although the clinical utility of these findings is uncertain, the line of investigation linking temperament to pharmacological treatment response is nevertheless promising. In a study of patients with a panic disorder or a generalized anxiety disorder (Wingerson et al., 1993), those dropping out were found to score significantly higher than those not dropping out on Novelty Seeking but not on other demographic or clinical variables. In conclusion, Harm Avoidance scores appear to be consistently elevated in non-responders to antidepressant treatment while paricular combinations of dimensions of temperament (e.g., Harm Avoidance and Reward Dependence) are not consistently related to treatment response. Clinical trials including measures of temperament, moreover, have primarily studied depressed patients and paid little or no attention to the differential effects of antidepressants (e.g., TCAs versus SSRIs).

The aim of the present study was therefore to examine the relation between temperament and response to an SSRI, fluvoxamine, and a TCA,

imipramine. Given that the different dimensions of temperament cut across the DSM categories of disorders, we included all patients who could be expected to respond to treatment with antidepressants and thus patients with either a mood or an anxiety disorder or a comorbid combination of such. Rather than focus on the DSM categorisations in terms of current symptomatology, we also explored temperament as a means of detecting subtypes of patients who may respond particularly well or particularly poorly to treatment. We hypothesised that patients with high Harm Avoidance would respond better to fluvoxamine than to imipramine. This assumption is based on the fact that Harm Avoidance is assumed to be more directly related to susceptibility to anxiety and/or serotonergic neurotransmission. In addition, the role of Reward Dependence and the interaction of this with Harm Avoidance will be explored. Those dropping out of treatment will also be considered in keeping with the assumption that noncompleters may produce higher scores on Novelty Seeking than completers.

Methods

Design

Patients with either a mood or an anxiety disorder according to the DSM-III-R were randomly treated with imipramine or fluvoxamine in a 6-week treatment study. To obtain a representative outpatient sample and avoid a selection bias, the treatment was not blind but the ratings of treatment outcome were. Patients visited the psychiatrist weekly for the first two weeks and every two weeks thereafter. The visits took an average of 20 minutes. No additional psychotherapy was given. The research psychologist administered the CPRS (Comprehensive Psychopathological Rating Scale; Åsberg, Montgomery, Perris, Schalling, & Sedvall, 1978) on the day which the patient started with the medication (baseline) and during the sixth week of treatment (week 6; outcome measurement).

Subjects

All newly attending patients between 18 and 65 years of age were screened for the DSM-III-R criteria for a mood or anxiety disorder. Patients with at least a moderate severity (4) of their illness according to the Clinical Global Impression (CGI: Guy, 1976) were included. The following exclusion criteria were next applied: a) contra indications for antidepressant drugs; b) unsuccessful treatment with fluvoxamine or imipramine during the present episode; c) treatment with another antidepressant within one week of randomisation and fluoxetine within five weeks of entering the study; d) concurrent use of CNS medication, other than for night-time sedation and to control anxiety; and/or e) use of psychedelics or alcohol on a daily basis (more than 3 drinks a day).

Treatment conditions

The patients were randomly selected to receive imipramine or fluvoxamine. The dosage for the fluvoxamine was 50 mg. the first day, to be increased to 150 mg/d at the end of the first week. A temporary decrease of the dosage due to side effects was allowed, but the dosage of 150 mg/d had to be reached within 14 days of the first treatment day. During weeks 2 through 6, a minimum dosage of 150 mg/d was maintained. During weeks 4 through 6, the dosage could be increased to a maximum of 200 mg/d in cases of nonresponse. The imipramine dosage started at 75 mg/d. After one week, blood was collected for blood level determination and assessed within five days. The dosages were adjusted to obtain blood levels of 200Fg/1 of the sum of imipramine and desmethylimipramine, which was checked at week 4. No concomitant medication was allowed, with the exception of oxazepam or lormetazepam during the first 4 weeks. During weeks 4 through 6, these benzodiazepines were not allowed.

Assessments

The Munich Diagnostic Checklists (MDCL) were used by the treating psychiatrists to screen for the DSM-III-R diagnoses (Hiller, Zaudig, & Mombour, 1990a, 1990b). The reliability of diagnoses based on the checklists has been found to be satisfactory (Hiller, Von Bose, Dichtl, & Agerer, 1990c). High agreement between raters has been obtained for major depression (k = .73) and for anxiety disorders as a whole (k = .76). Less agreement has been found for agoraphobia, social phobia and dysthymia. The MDCL enables clinicians to examine mental disorders in a systematic manner. For the present study, a subset of the checklists was used: adjustment disorder, agoraphobia, alcohol dependence and abuse, bulimia nervosa, dysthymia, generalized anxiety disorder, major depressive disorder, obsessive compulsive disorder, panic disorder, schizo affective disorder, simple phobia, social phobia and somatization disorder. The psychiatrist had to complete the full subset for all patients.

The Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987) was used to measure the different dimensions of temperament. Based on the assumption that temperament is relatively stable over time and for practical reasons, the TPQ was administered during the sixth week of treatment. In case of early dropout, we asked the patient to further co-operate and complete the TPQ.

To assess response to treatment, an instrument suitable for quantification of anxiety as well as depressive symptoms was needed. To this end, a composite of the subscales from the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al., 1978) was used for depression (MADRS) (Montgomery & Åsberg, 1979), for anxiety (BSA) (Tyrer, Owen, & Cicchetti, 1984) and for obsessive compulsive disorder (Thorén, Åsberg, Cronholm, Jörnestedt, & Träskman, 1980; Montgomery & Montgomery, 1980). These

composite scales have been specifically designed for treatment evaluation, and the MADRS in particular has been used extensively in pharmacotreatment studies. This composite scale (the 'mood-anxiety subscale' of the CPRS (CPRS-MA) consists of 21 items (18 symptoms and 3 observation items). The CPRS-MA is similar to the recently developed self-rating scale for depression and anxiety states (CPRS-S-A), which is based on the original CPRS (Svanvorg & Åsberg, 1994). The CPRS-S-A consists of 19 items. Seventeen items are the same as in the CPRS-MA with the item 'inner tension' from the CPRS-MA split into 'inner tension' and 'panic attacks.' Obviously, the 3 observational items are not included in the self-rating scale.

Statistical analysis

To examine the relationship between the treatment outcome measure (CPRS-MA) and temperament as measured by the TPQ, Pearson correlations were calculated. To explore the potential differences between the two treatment groups, regression analyses were performed with the CPRS-MA score at week 6 as the dependent variable. The general linear model included the CPRS-MA score at week 0 and Harm Avoidance, Reward Dependence and Persistence as independent factors. Assessments made more than 14 days difference from week 6 were excluded from any further analyses; a total of two measurements were excluded for this reason, which meant that the regression analyses were based on 61 of the 63 patients who completed the six weeks of treatment. The data were analysed with the aid of SPSS for Windows, release 7.5.2. The GLM General Factorial procedure was used for the regression analysis.

Results

A total of 74 patients started treatment. Sixty-three patients completed treatment and 11 (14.8%) dropped out. Of the 63 completers, the TPQ data for 61 patients was analysed in the end (see above). For 5 of the 11 dropouts, we were still able to administer the TPQ during week 6. The clinical characteristics of the completers and noncompleters are presented in Table 7.1.

Table 7.1 *Clinical characteristics of completers and noncompleters*

	Completers			Noncompleters		
	n	*M*	*SD*	*n*	*M*	*SD*
Age	61[a]	35.70	10.45	11	31.20	8.77
Male/female	24/37			4/7		
Imipramine	30			7		
Fluvoxamine	31			4		
DSM-III-R diagnosis:						
Mood disorder	15			1		
Anxiety disorder	27			8		
Mood and Anxiety disorder	19			2		
TPQ:						
Harm Avoidance	61	18.98	7.55	5	20.00	4.64
Novelty Seeking	61	15.65	4.14	5	19.00	4.12
Reward Dependence	61	13.15	3.36	5	13.80	4.76
Persistence	61	5.01	2.02	5	3.20	2.86

Note. [a] n = 61, completers included for analyses

The mean TPQ scale scores are presented in Table 7.1. As expected, the mean Harm Avoidance score (18.98) is elevated when compared to a normal population. Recently, Dutch norm scores for the Temperament and Character Inventory (TCI) have been reported (Duysens, Goekoop, Spinhoven, & Eurelings-Bontekoe, 1997) with a mean of 15.15 for Harm Avoidance, which is higher than the mean of 12.6 for an American norm group (Cloninger et al., 1994).

Harm Avoidance was significantly correlated with the CPRS-MA scores at week 0 ($r = .27$, $p < .05$) as well as at week 6 ($r = .40$, $p < .01$). In addition, the Persistence score was correlated with the CPRS-MA score at week 6 ($r = .25$, $p = .05$). No significant correlations were found for Reward Dependence or Novelty Seeking. The correlation coefficients for the dimensions of temperament were next considered per treatment group as shown in Table 7.2. Harm Avoidance correlated with the outcome score for both treatment groups while Persistence correlated with the outcome score for the fluvoxamine group only ($r = .42$, $p < .05$).

Table 7.2 *Pearson correlation coefficients (r) for TPQ scale scores with CPRS-MA outcome scores of all patients who completed treatment and per treatment group*

	total patients (n=61)		fluvoxamine (n=31)		imipramine (n=30)	
TPQ scale	week0	week6	week0	week6	week0	week6
Harm Avoidance	.27*	.40**	.27	.36*	.28	.49**
Novelty Seeking	.04	.04	.05	.01	.04	.15
Reward Dependence	-.02	-.03	-.15	-.14	.15	.13
Persistence	.06	.25	.11	.42*	-.02	-.11

Note. *$p < 0.05$, **$p < 0.01$

The regression analyses including treatment group, the CPRS-MA week 0 score, Harm Avoidance, Reward Dependence and Persistence as independent factors proved significant ($df = 5$, $F = 8.70$, $p < .001$) (see Table 7.3). Harm Avoidance ($F = 8.19$, $p < .01$) and Persistence ($F = 6.46$, $p < .05$) showed significant main effects on treatment outcome. No differences between the treatment groups were found.

To further explore the differences between treatment with fluvoxamine and imipramine, the interaction of Harm Avoidance with treatment group and Persistence with treatment group was included. The general linear model was significant ($df = 7$, $F = 6.92$, $p < .001$) and explained 47% of the variance. The main effect of Harm Avoidance remained significant ($F = 7.03$, $p < .05$), but the interaction with treatment group was not significant. Persistence showed no significant main effect, but the interaction with treatment group approached significance ($F = 3.64$, $p = .062$).

Table 7.3 *Regression analyses on TPQ scales and treatment outcome*

Model	Independent variables	*F*	*p value*	*F model*	*p model*
1[a]				8.70	.000***
	CPRS-MA baseline	16.96	0.000***		
	Harm Avoidance	8.19	0.006**		
	Persistence	6.46	0.014*		
	Reward Dependence	0.01	0.910		
	Treatment group	1.87	0.177		
2[b]				6.92	.000***
	CPRS-MA baseline	16.98	0.000***		
	Harm Avoidance	7.03	0.011*		
	Reward Dependence	0.14	0.711		
	Persistence	2.49	0.120		
	Treatment group	1.04	0.312		
	Harm Avoidance x Treatment group	0.01	0.915		
	Persistence x Treatment group	3.64	0.062		

Note. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[a] $n = 61$; *R Square* = .442; $df = 5$.

[b] $n = 61$; *R Square* = .478; $df = 7$.

The TPQ scale scores for completers versus noncompleters are presented in Table 7.1. Comparison of the completers with the noncompleters showed the dropouts to score higher on Novelty Seeking and lower on Persistence although not significantly (t-test; resp. t =-1.74, p = .08 and t =1.87, p = .06, resp.). No differences were found with regard to Harm Avoidance or Reward Dependence.

Discussion

The Harm Avoidance scores for our patient sample were found to be higher than for normals, which is in line with prior reports on patients with mood and anxiety disorders (Cloninger et al., 1994). Harm Avoidance negatively correlated with treatment response. While Joffe et al. (1993) observed a similar relation between Harm Avoidance and antidepressant treatment response in depressed patients, Joyce et al. (1994) obtained results to the contrary. The present sample of patients with mood and anxiety disorders was

analysed in terms of temperament because it was assumed that temperament factors would be more related than DSM classification to treatment response. Temperament was indeed found to play a role in treatment response although the assumption that high Harm Avoidance would be more specifically related to response to fluvoxamine was not confirmed.

Neither Reward Dependence nor Novelty Seeking related to treatment outcome. Non-completion of treatment appeared to be related to high scores on Novelty Seeking, which is similar to a previous report on patients with panic or generalized anxiety disorder (Wingerson et al., 1993). This also suggests a selection bias with regard to temperament characteristics when it comes to samples of patients completing experimental trials such as the present one.

A new finding is the relation of scores on the TPQ Persistence scale to treatment outcome. The Persistence scale was separated from the Reward Dependence scale only after introduction of the TPQ, which means that the Persistence items were originally included in the Reward Dependence scale (e.g., Joffe, et al., 1993; Joyce et al., 1994). In addition, the Persistence scale has not been included in analyses of response to antidepressant treatment in recent studies (Nelson & Cloninger, 1997). In the present study, high scores on the Persistence scale were correlated with low response to fluvoxamine but not to imipramine. The interaction between Persistence and treatment group approached statistical significance in the regression analysis. Low scorers on Persistence tend to be inactive, modest and give up easily. And such patients may respond preferentially to an SSRI than to a TCA regardless of their disorder being a mood or anxiety disorder according to the DSM criteria.

The present study was the first to compare the therapeutic effects of an SSRI versus a TCA in a group of patients with mood and anxiety disorders warranting antidepressant treatment. Further studies are certainly needed to confirm the present results, and a number of methodological issues should be addressed while doing this. We assumed the TPQ to be largely state-independent and therefore administered it during week 6 of treatment. It has nevertheless been reported that Harm Avoidance in particular may be state dependent (Cloninger et al. 1994; Chien & Dunner, 1996; Strakowski et al., 1995). In addition, we used an outcome scale which closely resembles the self-rating scale developed by Svanvorg and Åsberg (1994) but has yet to be validated: the CPRS-MA. The number of patients included in the analyses in the present study tended to be rather small although this does not alter the heuristic value of the present findings. Assignment to treatment condition was random but not blind in the present study, which could result in an assessment bias, although the outcome scale was scored by a judge blind to treatment condition. Patients who would otherwise have refused to participate in a double blind study were presumably included in the present study, which could be at the basis of the present results. Finally, treatment with imi-

pramine was blood level controlled. This avoided the usual problem of undertreatment or high dropout rates due to side-effects. Given that the detection of a relation of treatment effects to other variables may critically depend on optimal dosing, the blood level control may also be significant with regard to the results obtained (Bruijn et al., 1999).

In conclusion, the present study showed an inverse relation of Persistence with treatment response to fluvoxamine but not to imipramine. It also confirmed an inverse relation between Harm Avoidance and treatment response to both antidepressants. Previous findings on the role of particular combinations of the different temperament dimensions (i.e., types of temperament) in response to treatment with antidepressants have not been supported. Further studies are nevertheless needed to confirm these findings, particularly in light of the new methods utilised in this study.

Note. Submitted for publication

8 General discussion

The present thesis was an exploration of how to detect differences in antidepressant treatment response in patients with mood and anxiety disorders. The efficacy of TCAs and SSRIs for the treatment of mood as well as anxiety disorders is generally accepted. Nevertheless, it is still not possible to predict antidepressant treatment response with accuracy and to differentiate meaningfully between TCAs and SSRIs. The current empirical evidence is limited to showing a favourable response to TCAs in severely depressed patients. The presupposed favourable response to SSRIs in patients with anxiety disorders has not been confirmed by empirical research. In other words, meaningful differences between treatment with SSRIs versus TCAs have not been found in less severe patients, classified with either a mood disorder or an anxiety disorder. Such patients are characterised by a high level of comorbidity, and the currently accepted DSM classification system does not suitably distinguish mood and anxiety disorder patients. As a consequence, the DSM criteria are also not suitable for the selection of subtypes of patients who may show a favourable treatment response to either TCAs or SSRIs.

In the present study the value of alternative classification models was therefore explored to detect any differences in the efficacy of SSRIs and TCAs which may have gone undetected using the current DSM classification system. First, classification of patients according to primary diagnosis was explored. Patients with a primary anxiety disorder (i.e., anxiety disorder as the first disorder in their lifetime) were assumed to respond favourably to an SSRI, while patients with a primary depression were assumed to respond favourably to a TCA. Patients can also be classified according to personality factors or temperament, which have been shown to be related to the prediction of antidepressant treatment response. The personality model of temperament put forth by Cloninger is also therefore included in the present study. Finally, it should be noted that the patients included in research are usually selected on the basis of a single DSM diagnosis. In light of the frequent comorbidity of mood and anxiety disorders, however, a clear bias towards the patient selection may exist. Conversely, possible differences between treatments may go undetected as a result of the confounding of mood and anxiety disorders within a single diagnosis. To avoid such a selection bias, all patients who might benefit from antidepressant treatment were included in the present study; this thus included patients with mood disorders, anxiety disorders, or both.

To summarise, the basic aim of the present study was to reduce selection bias and include all patients who might benefit from antidepressant treatment based on current symptomatology, patients thus meeting the DSM criteria for mood disorder and/or anxiety disorder. The patients were then classified according to primary diagnosis and temperament in order to tho-

roughly explore any differences in treatment response to TCAs and SSRIs. The main issues of the present study will be discussed in the current chapter.

8.1 The impact of comorbidity on patient selection

The DSM classification of mood and anxiety disorders as separate disorders is often artificial in clinical practice. Nevertheless, the DSM criteria are widely accepted for the selection of patient samples in treatment outcome research. Due to the high co-occurrence of mood and anxiety symptoms, patients often may fulfil criteria of both disorders. Patient selection procedures, therefore, contribute to the empirical evidence of the outcome results. The following questions are poorly described in re-search reports and especially clinical trials: How were patients recruited? What diagnostic procedure was used (clinical judgement or structured clinical interview)? Who selected the patients (the treating clinician, an independent assessor)? And, how many and which of the suitable patients finally entered the study? In an attempt to cope with the comorbidity of mood and anxiety disorders, exclusion rules for the omission of patients with comorbid disorders are common. Nevertheless, only those patients with clearly comorbid disorders are typically excluded which means that cases with less severe comorbid symptoms are still included.

The current study therefore included all patients with mood as well as anxiety disorders in order to limit the effects of a possible selection bias due to comorbidity. The diagnostic procedure for the selection and inclusion of patients was semi-structured with the use of the Munich Diagnostic checklists (MDCL) which allowed the psychiatrists to make a more accurate diagnosis. Furthermore, a fully standardised instrument (the Composite International Diagnostic Interview: CIDI) was administered by a psychologist who was not involved in the regular treatment of the patients. The comparison of psychiatric diagnosis and CIDI diagnosis confirmed the confounding role of comorbidity. Clinicians tend to choose either a mood disorder or an anxiety disorder, even though the DSM criteria for both are met when assessed with the CIDI. Of the DSM-III-R categories, agreement was found to be best although no more than moderate for major depression, and lowest for generalized anxiety disorder. These findings are in line with the assumption that a subgroup of major depressed patients can be clearly detected and probably constitute the most severe cases. A lot of patients nevertheless present with a mixture of mood and anxiety symptoms, such as in generalized anxiety disorder. In line with other comorbidity research, half of the patients in the present study showed a comorbidity of mood and anxiety disorders as assessed by the CIDI standardised instrument. In these patients, problems thus arise when a differential diagnosis has to be made and a distinct diagnostic category must be assigned.

The present findings illustrate the selection bias which can occur in studies with a focus on only patients with a mood disorder or an anxiety disorder. By including both patient groups, selection bias due to the tendency of clinicians to opt for either a mood or an anxiety disorder was avoided. They nevertheless entered the study.

8.2 The consequences of diagnostic procedures for the outcomes of clinical trials

The current finding of low agreement when two independent diagnostic procedures are used has important implications for the validity of psychiatric diagnosis. In addition, most treatment outcome studies with antidepressants make use of the DSM criteria for patient selection even though the differentiation of mood and anxiety disorders remains a problem within the DSM classification system. As a consequence, patient selection is dependent on the diagnostic procedures used by the clinicians.

In the present study, the selection of the patients started with screening by a psychiatrist for the presence or absence of an affective disorder (either a mood or anxiety disorder based on the DSM criteria). For the group of patients meeting the DSM criteria for an affective disorder, the agreement between the psychiatric diagnosis and the CIDI diagnosis turned out to be low. Clinicians tend to assign a diagnosis of either a mood disorder or an anxiety disorder in line with the clinical tradition of making a single diagnosis. This occurred despite a lack of consistent rules for how to differentiate between mood and anxiety disorders and suggests that inclusion based on a diagnostic procedure other than the psychiatric diagnosis as assessed with the Munich Diagnostic Check Lists, which we used, may have produced a very different patient group. Depending on the diagnostic category assigned to a patient, the patients will be either included or not included and the treatment results thereby influenced. DSM categorisation fosters artificial differentiation of mood and anxiety disorders and the value of outcome studies using separate diagnostic categories is limited due to the use of different inclusion procedures and thus little comparability. Therefore it is of main importance to raise consensus on how to differentiate between categories of mood and anxiety disorders and how to use inclusion and exclusion rules. The inclusion of patients solely on the basis of a psychiatric diagnosis further complicates the interpretation of treatment results as the accuracy of the diagnosis is of critical importance for the study of treatment outcome. The use of standard procedures for clinical diagnosis is therefore recommended in outcome research (also not restricted to pharmacotreatment).

8.3 The role of primary diagnosis in antidepressant treatment response

The problem of differentiating response to TCAs and SSRIs is also related to the existence of comorbidity. We assumed diagnosis at first episode in a patient's lifetime to be of greater value for the differentiation of mood and anxiety disorders in line with the work of Cloninger (1990) and Winokur (1997). The primary/secondary distinction is based on the development of the syndrome rather than on current symptomatology. Research on the sequential relationship of mood and anxiety disorders has shown primary depression to rarely change into an anxiety disorder while the occurrence of secondary depression in patients with an initial anxiety disorder (also named demoralisation depression), is rather common. These findings suggest the existence of different disease processes and potentially different etiological bases for different subtypes of mood and anxiety disorders.

In the present study, the role of primary diagnosis in treatment response to TCAs and SSRIs was explored. The assumption that patients with a primary depression respond better to a TCA (imipramine) while patients with a primary anxiety disorder respond better to an SSRI (fluvoxamine) was supported to some extent. Patients with a primary depression showed a better response to imipramine than to fluvoxamine at week2 but not at week6 for both of the outcome measures, the CPRS-MA and CGI, respectively. In other words, the initial response to imipramine is better than the initial response to fluvoxamine in patients with a primary depression. The findings were stronger for the subgroup of patients with a primary depression and no comorbid anxiety disorder. Comparison of the group means for the CPRS-MA items specific to mood disorders or anxiety disorders showed patient improvement to not be restricted to certain symptoms. These results show clear improvement within the first two weeks of treatment with imipramine for primary depression. This temporary difference from the response to treatment with fluvoxamine may be a result of the increased symptoms of arousal which is often interpreted as being a side-effect of fluvoxamine (Den Boer & Westenberg, 1988).

Patients with a primary anxiety disorder, in contrast, showed a better response to fluvoxamine for only the CGI outcome measure. The origin of the differences in the results for the CPRS-MA and CGI measures can only be guessed at, however. The differences may stem from the psychometric properties of the scales, such as variation in the sensitivity and specificity of the scales to the different subgroups of patients. Given our focus on patients with any DSM-III-R diagnosis of mood or anxiety disorder, we needed an outcome measure sensitive to a wide range of symptoms, including both mood and anxiety symptoms. The existing outcome measures, such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) or the Clinical Anxiety Scale (CAS) (Snaith, Baugh, Clayden, Husain & Sipple, 1982), did not meet this need. We therefore adopted a composite scale

composed of the depression, anxiety and OCD items from the CPRS (CPRS-MA) as the best possible outcome measure available at this point. Although comparable to the CPRS-S-A (Svanborg & Åsberg, 1994), this scale has not been validated and we therefore also decided to use the CGI, a general measure of improvement not related to specific symptoms. The fact that the patients with a primary depression were found to have higher baseline scores on the CPRS-MA when compared to the patients with primary anxiety suggests a lack of balance in the items constituting this measure. Indeed, mood symptoms appeared to be measured more extensively than anxiety symptoms; for example, experience of panic attacks is included under the item 'inner tension'. For the CPRS-S-A (Svanborg & Åsberg, 1994), in fact, the experience of panic attacks has been added as a separate item for this very same reason. This lack of balance in the items may also suggest that the CPRS-MA is not sufficiently sensitive to detect treatment differences in patients with primary anxiety disorder. Indeed, only the results based on the CGI showed favourable response to fluvoxamine in patients with primary anxiety disorder. In conclusion, the CPRS-MA appears to be a more sensitive measure to assess treatment response in patients with primary depression than in patients with primary anxiety disorder. Nevertheless, it is also possible that indeed a difference in the severity of the primary depression versus primary anxiety disorder exists. The present results should therefore be considered preliminary and more research with the CPRS-MA is mandatory to be applied for the same purpose in future studies.

The operationalisation of the primary-secondary distinction to discern subtypes of mood and anxiety disorders also raised some difficulties. We used the CIDI to measure lifetime diagnosis but this has the problem of retrospective assessment. The extend to which primary depression and primary anxiety disorder may have been classified incorrectly in retrospect remains to be investigated. At this moment, there seems to be no clear solution to this problem except for prospective study. Some support for the validity of the CIDI to assign primary diagnosis is provided in the present study in that response differences to imipramine and fluvoxamine became most apparent in patients with a primary depression without comorbid anxiety disorder. These patients may be the 'pure' melancholic depressions and are compared to primary anxiety disorder patients who may develop a secondary depression at a later stage. The existence of a first episode consisting of a mood disorder and an anxiety disorder at the same time needs further investigation. In addition to this, the CIDI may not be adequate for distinguishing the onset of DSM disorders particularly when the disorders appear relatively close to each other over time. The value of retrospective assessment clearly depends on the recall of the patients and recalling the time of onset of symptoms may be particularly difficult when numerous symptoms appear within a certain period of time.

Three additional methodological issues should be noted at this point. The validity of our inclusion criterion, namely a CGI score of at least moderate severity (score 4) needs to be considered. With interrater sessions under the supervision of a psychiatrist who did not participate in treatment, we aimed to raise the degree of agreement on this measure. Furthermore, although the study was not double-blind, the raters were blind to which of the treatments the patients were assigned to. Finally, in contrast to most other trials, we used therapeutic drug monitoring (TDM) to determine the appropriate dosage of imipramine. This strategy circumvents the problem of overly aggressive dosages which can lead to high dropout rates, or suboptimal dosages of imipramine. The use of TDM may also, thus, be related to the efficacy of imipramine.

In conclusion, and despite the methodological problems yet to be solved, the paradigms used in the present study to differentiate treatment response to a SSRI from response to a TCA appears to be promising. The findings are fairly consistent with the initial assumptions we made, namely that patients with a primary depression will respond better to imipramine while patients with primary anxiety disorder will respond better to fluvoxamine. The results suggest that the information on the nature of the first illness episode may be more valuable than the categorisation as a current DSM mood or anxiety disorders. Support is also thus provided for the relevance of distinguishing between a primary versus secondary depression (Cloninger et al., 1990; Winokur, 1997) to predict antidepressant treatment response. In the words of Klerman: "The growing acceptance of operational criteria has led to widespread dissatisfaction with the existing system, because of the exclusive reliance on clinical symptomatic and behavioural features. The search for pathological processes remains a fervent hope of many investigators. They accept the high level of comorbidity as a starting point and look to genetics, physiology, stress and personality dynamics for underlying mechanisms that would explain and unite the diverse comorbid states" (in: Maser & Cloninger, 1990, p. 37).

8.4 The role of temperament in antidepressant treatment response

The psychobiological personality model of Cloninger has been reputed to differentiate responders from nonresponders to antidepressant treatment (Cloninger et al., 1994). The four temperament dimensions of Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence are postulated to reflect underlying biogenetic variations in dopaminergic, serotonergic and noradrenergic brain systems. And the aforementioned dimensions of temperament appear to be related to susceptibility to different neurotic syndromes (Cloninger et al., 1993). Harm Avoidance is postulated to reflect variations in serotonergic activity and empirical findings show Harm Avoidance scores

to be consistently elevated in patients with mood and anxiety disorders when compared to the normal population (Brown et al., 1992; Cloninger et al., 1994; Cowley et al., 1993; Joffe et al., 1993). Whereas high Novelty Seeking in combination with high Harm Avoidance is assumed to be related to dysthymia as a result of the continual approach-avoidance conflicts within the person, high Novelty Seeking in combination with low Harm Avoidance is associated with impulsive-aggressive behaviour. Finally, high Reward Dependence has been related to the development of atypical depression (Cloninger et al., 1994). Cloninger concluded that depressives are clinically and etiologically heterogeneous and that temperament is a more powerful way of characterising these people than depressive symptoms and co-morbid psychopathology. In line with this, the present study focused on patients with a mood and/or anxiety disorder and explored the role of temperament in their response to treatment with a TCA or SSRI. Temperament was used to identify subgroups of patients and the scores determined with the aid of the Tridimensional Personality Questionnaire (TPQ) were found to be consistent with those in prior reports (Cloninger et al., 1994). Harm Avoidance scores were elevated when compared to normals. Furthermore, patients with high Harm Avoidance showed poorer treatment response although their scores did not differentiate between imipramine and fluvoxamine. Earlier findings regarding the role of Reward Dependence and the effects of an interaction between Harm Avoidance and Reward Dependence on treatment outcome were not confirmed.

It should be noted that the results regarding Harm Avoidance may be an artefact of state dependency. Harm Avoidance scores may be temporarily elevated as a result of depressive or anxious feelings as part of the disorder rather than a more permanent personality trait, and Harm Avoidance has indeed been found to be related to current mood state (Chien & Dunner, 1996; Joffe et al., 1993). In the present study the Harm Avoidance scores, measured at week6 of treatment, were found to signifycantly decrease in responders but not in nonresponders while the Novelty Seeking and Reward Dependence scores did not change. Difficulties with the measurement of trait characteristics due to interference of current psychopathology are frequently acknowledged but no conclusive solution is available. Based on the theoretical assumption that temperament dimensions remain stable, we examined the TPQ at week 6 but still may have measured the state effects of depressive symptomatology. In future studies, the assumed influence of state mood effects on temperament scores must be ruled out. As long as the scores are state dependent, prediction of treatment outcome based on dimensions of temperament has limited value. In any case, temperament should preferably be measured at baseline. Best, of course, is to assess temperament twice, before and after treatment, in order to explore any changes in temperament scores during treatment.

The role of Persistence also needs further explanation. Persistence was originally a subscale of Reward Dependence but turned out to be a separate fourth dimension of temperament. In line with this, the Persistence items have been excluded from Reward Dependence in more recent studies (e.g., Nelson & Cloninger, 1997). We found, as postulated a-priori, a differential role for Persistence in response to treatment with fluvoxamine versus imipramine (i.e., patients with lower scores on Persistence responded better to fluvoxamine than patients with higher scores) while no such differences were found for the imipramine group. According to the model of personality used in the present study, Persistence is viewed as a tendency to be hard working, stable and industrious (Cloninger et al., 1994). Low scorers on Persistence are viewed as inactive, modest and tending to give up easily. The question, then, is what may link low Persistence to a better response to treatment with an SSRI? At first sight, it would be expected that high Persistence improves treatment outcome for both groups due to a tendency to active participation and compliance with the treatment. An alternative psychological explanation is that a low score on Persistence indicates a need for help or dependence on help. The dependent personality characteristics may then help explore which types of mood and anxiety disorders respond best to SSRIs. These preliminary findings on the role of Persistence in treatment outcome need to be further investigated in future research, however.

In conclusion, the present study showed, consistent with prior reports, a negative relation of Harm Avoidance to antidepressant treatment response. However and contrary to our initial assumption, no differentiation between fluvoxamine and imipramine was found. Furthermore, Persistence turned out to be related to fluvoxamine response. The present data provide support for the role of temperament based on the personality model of Cloninger in antidepressant treatment response although the ability of temperament to differentiate between response to TCAs and SSRIs needs further exploration.

8.5 Limitations of the present study

The present study constitutes an initial attempt to differentiate response to antidepressants using a different design than in most outcome studies. The inclusion of patients with any DSM-III-R diagnosis of mood or anxiety disorder and use of the alternative concepts of primary diagnosis and temperament nevertheless raises the following methodological problems.

1. *Use of the CPRS-MA as an outcome measure*. As already pointed out, inclusion of patients with mood as well as anxiety disorders meant that the regular outcome measures did not suffice. No fully validated outcome measures were available to assess both mood as well as anxiety symptoms, so it was decided to compose a composite subscale of the CPRS,

the CPRS-MA, which includes the items form the depression, anxiety and OCD subscales. The CPRS-MA was thus used as the main outcome measure along with the CGI, a global clinical measure. As already discussed, the CPRS-MA turned out to be higher at baseline for patients with a primary depression when compared to patients with a primary anxiety disorder. This suggests that the CPRS-MA is also not sufficiently sensitive to detect differences in patients with primary anxiety disorder. Validation of the CPRS-MA is therefore needed before further use in similar studies.

2. *Assessment of primary diagnosis*. As discussed in section 7.2, the operationalisation of primary diagnosis raised some problems. The chronology of lifetime diagnoses is assessed retrospectively, which limits the reliability and validity of this measure. Information regarding the temporally onset of mood and anxiety symptoms at first episode appears to be particularly important for distinguishing primary depression from primary anxiety disorder patients. In the present study, 18 of the 40 patients in the primary depression group had a co-occurring anxiety disorder at first episode. The decision to include patients with both a mood and anxiety disorder at first episode in the primary depression group may thus be arbitrary, although we assumed that the anxiety symptoms were an epiphenomena of the mood disorder. The CIDI provides lifetime diagnosis but gives no information on the onset of the separate mood and anxiety symptoms within the first episode, which would be helpful to further distinguish primary depression versus primary anxiety disorder. Given that the treatment response differences were most clear for the subgroup of patients with primary depression without a comorbid anxiety disorder, the comorbid group may indeed be more heterogeneous. The assessment of the onset of the first episode of a mood or anxiety disorder in a person's lifetime should therefore be specified in future research as well.
3. *Assessment of temperament*. At the time at which the present project was initiated in 1994, we considered temperament a personality trait and in line with this theoretical concept, relatively stable throughout life. From this perspective the time at which the TPQ was administered seemed irelevant. Because the study was conducted in a community mental health centre (RIAGG) and our research protocol had to be followed with respect to the usual clinical practice, concessions were made. It was decided to administer the TPQ after six weeks of treatment due to the limited time available for assessment at baseline. For the same reasons, the CIDI was administered after four weeks of treatment. It is now known that at least in the case of mood disorders Harm Avoidance scores do not remain stable during treatment and that the *state* of the individual at the time of assessment may influence such scores, which clearly limits the utility of Harm Avoidance scores for the prediction of treatment response. In further outcome research it is also therefore recommended that the TPQ be

administered at baseline as well. In such a manner, the stability of temperament during treatment can be assessed and explored for different subgroups of patients with mood and/or anxiety disorders. If patients with (primary) mood disorders indeed show indeed less stable patterns during treatment than patients with (primary) anxiety disorders, this may indeed be an indication of differences in antidepressant treatment response. From this perspective, it is important to determine whether temperament scores changes solely as a result of treatment (e.g., the reduction of symptoms) or not, and whether this is different for mood versus anxiety disorders. Otherwise, for example, high Harm Avoidance scores may still be viewed as no more than an epiphenomenon of severity, which is known to be related to antidepressant treatment outcome.

Another issue is the difficulty patients were found to experience with the administration of the TPQ. The TPQ consists of 100 true/false items to be completed in about 20 minutes. Several patients reported difficulties concentrating and asked for help on several questions. The psychometric properties of the American version of the questionnaire have been found to be adequate. The Dutch version of the TPQ, however, has not been validated. In this light, it is certainly possible that the difficulties we experienced are in line with some more general discrepancies between American and European clinical research. Clinical trials are often contradictory due to differences in the clinical material, methodologies, health service systems, psychiatric traditions and types of patients used (Ansseau, 1992). Our patient sample was recruited from a community mental health centre where research was rather uncommon and as little interference in the regular clinical practice was made as possible. Psychometric research on the dimensions of temperament within a Dutch population has been initiated with the latest version of the TPQ, the TCI (Duijsens, Goekoop, Spinhoven & Eurelings-Bontekoe, 1997). Validation within psychiatric populations, outpatients as well as inpatients, is of particular interest although not yet available.

4. *Selection bias*. To include a wide range of patients in line with regular clinical practice and also prevent a selection bias due to the comorbidity of symptoms, the selection procedure was monitored. Extensive description of the inclusion procedure was available and regularly discussed in research meetings to prevent arbitrary selection. Nevertheless, our goal of selecting a broad patient population was only realised in part. Because we studied a clinical population from a community mental health centre (RIAGG), the study was restricted to outpatients. A multi-centre study with the inclusion of also more severely depressed inpatients is preferable to examine the role of primary diagnosis to detect relevant subtypes of depression and has recently been started. It is expected that the distinction between primary and secondary depression for inpatients will be more closely related to differential treatment response than for less severe ca-

ses. It should be noted, however, that the inclusion of inpatients raises new selection problems. Depressed inpatients tend to have a history of nonresponse to earlier treatments which can clearly influence the current treatment response (Bouvy, 1997) and complicate the comparison of the patient groups in multi-centre trial. It may therefore be preferable to include all patients from the same institution offering both ambulatory and inpatient care in an attempt to obtain a more or less un-biased patient group, although the diagnostic and treatment choices of the general practitioner prior to admittance may still influence the treatment results.

Patient sample size. During the screening period of two years, 564 patients were diagnosed with either a mood disorder or anxiety disorder. In the end, 98 of the patients (17%) entered the study and 92 of them (16%) actually started treatment. Most cases met one of the exclusion rules. Nevertheless, in one out of five cases no reason for exclusion could be traced which supports the assumption that at least part of these patients in fact should have been included in the study. The relatively small sample finally entering treatment in the present study illustrates the common problem of reaching large sample sizes in clinical research. It also illustrates the difficulty of obtaining a patient group representative of clinical practice. We also made choices within the selection procedure and our sample is only representative of patients fitting the inclusion and exclusion rules. Yet, another six patients were later excluded because they did not start the antidepressant treatment, which further reduced the comparability of our sample with those in other clinical trials. As already discussed, consensus must be reached on how to use the diagnostic categories and selection criteria in studying patients with affective disorders (mood or anxiety disorders). Furthermore, the patient samples we analysed did not include all treatment noncompleters because CIDI diagnosis and TPQ scores were not available for most dropouts, which may introduce a selection bias. We can not assume the noncompleters to be an a-selective sample based on diagnoses, clinical and personality characteristics.

In our attempt to detect meaningful underlying typologies within the spectrum of mood and anxiety disorders, a larger patient population would have been preferable. At this point, the analyses of the primary depression group without comorbid anxiety are limited by our small sample size. With regard to the role of temperament, our findings on patients who did not complete treatment, or dropouts, were limited although consistent with prior reports. The role of the combinations of dimensions of temperament, or temperament types in antidepressant treatment response certainly merits further study with larger patient samples.

8.6 Suggestions for further research

Because the present study constitutes an initial exploration of the role of primary diagnosis and the role of temperament in TCA and SSRI treatment response, replication of our findings is needed before they may have implications for treatment guidelines. Some suggestions for further research are as follows.

1. To overcome the comorbidity problem in outcome research, an outcome measure suited to the wide spectrum of mood and anxiety disorder patients should be developed. Further study with the CPRS-MA seems promising. The mood and anxiety items should be brought into better balance and the validity of the scale should be examined.
2. In addition to the need to verify temperament as a possible predictor of response to antidepressants, further research into the influence of current mood state on putatively stable temperament scores should be undertaken. For this purpose, exclusion of those items correlating highly with current mood state (indicated by the severity measures of mood and anxiety) to explore the stability of the remaining scores over time and their relation to treatment outcome is a possibility.
3. As discussed before, the assessment of primary diagnosis raises problems because the data must be collected retrospectively. Given that primary diagnosis appears to be a promising predictor of antidepressant treatment response it is important to search for objective measures that distinguish (primary) mood disorders and (primary) anxiety disorders. For this purpose, an experimental design taking current evidence showing memory bias in patients with major depression but not an anxiety disorder may be welcome (Bootzin & McKnight, 1998; Gotlib & Krasnoperova, 1998; MacLeod & Mathews, 1991). If differences in cognitive information processing are confirmed, a valuable objective measure becomes available to distinguish mood and anxiety disorders, apart from DSM classification. In addition, the detection of consistent differences in memory bias depending on primary diagnosis suggests that diagnosis at first episode in a patient's lifetime may not no longer be omitted from any diagnostical procedures. Finally, greater information on treatment response to TCAs versus SSRIs is still needed to facilitate the choice of antidepressants and enhance treatment efficacy as a result.

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Summary

Mood and anxiety disorders are the most prevalent psychiatric disorders. The symptoms of mood and anxiety disorders also frequently co-occur. In the present thesis, the implications of comorbid mood and anxiety disorders for the accuracy of psychiatric diagnosis and the implications of such comorbidity for treatment with antidepressants will be explored. The past three decades have witnessed considerable progress in the pharmacological treatment of mood disorders. The efficacy of antidepressants has not been restricted to mood disorders, however. Patients with anxiety disorders also appear to benefit from treatment with antidepressants. Even though there is a growing knowledge of the efficacy of different antidepressants and their range of utility, it is still not possible to predict with accuracy response to antidepressants in mood and anxiety disorders, or to find meaningful differences between antidepressants. Apart from evidence that tricyclic antidepressants (TCA) are probably more effective for the treatment of severely depressed patients, no differences in the efficacy of TCAs versus SSRIs (selective serotonin reuptake inhibitors) have been found for the treatment of mood and anxiety disorders. The present research is therefore an attempt to detect any differences in the efficacy of different antidepressants.

Chapters 1, 2 and 3 provide a theoretical introduction to the empirical research presented in subsequent chapters. Chapter 1 provides a general introduction and addresses the main research questions. The existence of comorbidity between mood and anxiety disorders is an important issue for the interpretation of treatment outcome although often ignored. Appropriate classification of mood and anxiety disorders remains difficult due to widespread comorbidity. The criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) as formulated by the American Psychiatric Association do not adequately distinguish these patient groups although the DSM categorises mood and anxiety disorders as separate disorders. In fact, the existing overlap in mood and anxiety symptoms raises the question of whether mood and anxiety disorders actually constitute different syndromes or are part of one and the same syndrome. In addition, when different antidepressants (e.g., TCA versus SSRI) are studied with presumably 'pure' groups of patients with a mood or anxiety disorder, the question remains as to whether the treatments really have the same effect when they do not produce significantly different results. Whether the patient recovers from only a mood disorder, co-existing anxiety symptoms or vice versa is simply unknown. In other words, possible differences in the effectiveness of antidepressants may go undetected because the patient selection was based on the DSM criteria for mood and anxiety disorders. That is: The DSM is widely accepted but classification according to the DSM has not resulted in the

identification of proper patient groups for treatment with specific antidepressants.

The aim of the present research is also, therefore, to examine response to treatment with TCAs versus SSRIs within a broad range of patients suffering from either a mood disorder, an anxiety disorder, or both. In doing this, the selection bias associated with the use of single diagnostic categories is presumably reduced. Alternative models for the identification of subgroups of patients responding differentially to antidepressant treatment were explored. Of particular interest were the role of primary diagnosis and the role of temperament. The use of systematic diagnostic procedures for the selection of the patient sample was also of particular interest. The present research thus had two main areas of interest: 1) diagnostic accuracy for mood and anxiety disorders (see Chapter 5) and 2) antidepressant treatment response (see Chapters 6 and 7).

In Chapter 2, the issues regarding the comorbidity of mood and anxiety disorders are considered in greater detail along with the implications of certain issues for research. In the present thesis, the term comorbidity refers to the situation in which more than one psychiatric disorder can be diagnosed in the same person. The rates of observed comorbidity have been found to differ enormously across studies from 15% to 91%. Such differences may be due to variability in the definition of the concept, sample selection, study time span and the assessment instrument. Along these lines, an anxiety disorder is more likely to precede a mood disorder than the reverse, and anxiety disorders are associated with an elevated risk of a mood disorder later in life. Finally, when mood and anxiety disorders co-occur, they tend to be associated with more severe symptoms, greater impairment, more chronic illness, poorer treatment outcome and a higher incidence of suicide.

The focus of Chapter 3 is on the personality model of Cloninger and the model of temperament in particular. Temperament refers to the individual differences in the automatic emotional reactions and habits of people. The model includes four dimensions of temperament: Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence. The theoretical model and corresponding inventory, the Tridimensional Personality Questionnaire (TPQ), are considered in greater detail in Chapter 3. The personality model of Cloninger has been reputed to differentiate between responders and non-responders to antidepressant treatment. For example, high scores on Harm Avoidance have been found to be related to nonresponse to antidepressant treatment. In the present research, the model of temperament is therefore included to explore the responses of patients with mood and/or anxiety disorders to treatment with a TCA versus a SSRI. Rather than a focus on the DSM categories based on current symptomatology, moreover, the personality model of Cloninger provides an alternative typology of patients based on temperament.

Chapter 4 provides an outline of the empirical research project on which the results presented in the subsequent chapters are based. Special attention is paid to the patient selection procedures, clear consideration of the excluded cases and the sample sizes analysed to answer the different research questions.

In Chapter 5, the results regarding diagnostic accuracy for mood and anxiety disorders are presented. More specifically, diagnoses based on clinical judgement were compared to diagnosis based on a structured diagnostic interview in patients with mood and/or anxiety disorders. The Munich Diagnostic checklists (MDCL) were used by the psychiatrists to establish the DSM-III-R diagnoses. The psychologists administered the Composite International Diagnostic Interview (CIDI) to establish the DSM-III-R diagnoses. The results showed only moderate agreement between the clinical diagnoses of mood and anxiety disorders and the CIDI-based diagnoses. Major depression showed the greatest degree of agreement although no more than moderate. Poor agreement was found for generalized anxiety disorder. Furthermore, comorbidity between mood and anxiety disorders was found to be common when assessed using the CIDI while the psychiatrists tended to diagnose either a mood disorder or an anxiety disorder. This finding suggests that comorbidity may not be the focus of attention for many clinicians and shows that important differences in the diagnosis of mood and anxiety disorders occur when different diagnostic procedures are followed. Such inconsistency poses not only a problem for the interpretation of research results but also for the generalisation of outcome results for both psychological and pharmacological treatment purposes.

In Chapter 6, the role of primary diagnosis (i.e., diagnosis at first episode) in antidepressant treatment response is considered using a design which was different than for most clinical trials. To avoid bias due to comorbidity, patients with any DSM-III-R diagnosis of a mood or anxiety disorder for which antidepressant treatment was indicated were included. Response to treatment with a TCA (imipramine) or an SSRI (fluvoxamine) was initially evaluated for this group as a whole (i.e., across mood and anxiety symptoms). For this purpose, a composite scale with the depression, anxiety and OCD items from the CPRS (CPRS-MA) was used. The CPRS-MA has yet to be validated, and we therefore used the Clinical Global Impression (CGI) to gain an overall impression of patient improvement independent of specific symptoms. For the patient group as a whole, no differences in the efficacies of the treatments with fluvoxamine or imipramine were observed. For subsequent analyses, the patients were grouped according to their first illness episode. The CIDI was used to assess whether the first episode was a mood disorder (primary depression) or an anxiety disorder (primary anxiety disorder). Support for the hypothesis that imipramine is more effective for the treatment of primary depression and fluvoxamine is more effective for the

treatment of primary anxiety disorder was found. Patients with primary depression responded better to imipramine at week 2 (but not at week 6), according to both the CPRS-MA and the CGI. Patients with primary anxiety disorder, in contrast, responded better to fluvoxamine, according to the CGI but not the CPRS-MA. Given the exploratory nature of the present study, replication of our findings is still needed. The differences in the results using the CPRS-MA and the CGI are discussed along with some limitations on the present study. The results suggest that information on the nature of the first illness episode may provide more valuable information than the current DSM classification as a mood or anxiety disorder, which underlines the importance of differentiating between a primary versus secondary depression for the prediction and analysis of treatment response.

In Chapter 7, the role of temperament in the response of patients to antidepressant treatment is considered. Based on the assumption that temperament is more related to antidepressant treatment response than DSM diagnoses, the present sample consisted of patients with a mood disorder, an anxiety disorder, or both. The hypothesis was that patients with high Harm Avoidance scores would respond better to fluvoxamine than to imipramine. This is because Harm Avoidance is assumed to be associated with a heightened susceptibility to anxiety and/or serotonergic neurotransmission. The main finding was that Harm Avoidance was indeed related to antidepressant treatment response but did not distinguish between imipramine and fluvoxamine. A number of important methodological issues are raised, including the assessment of temperament at 6 weeks rather than at baseline. While Harm Avoidance was assumed to be a relatively stable personality trait, it appeared to be related to current mood, which has clear implications for the interpretation of treatment results.

Finally, in Chapter 8, the major results of the present research are discussed along with some methodological limitations arising from the use of new paradigms to differentiate response to antidepressant treatment. The use of the CPRS-MA as an outcome measure, the assessment of primary diagnosis, the assessment of temperament, and selection bias are discussed. The chapter ends with some suggestions for further research. The present research was a first attempt to differentiate antidepressant treatment response with a design different from that used in previous clinical trials. Replication is therefore necessary before recommendations for clinical practice can be made.

Samenvatting

Stemmingsstoornissen en angststoornissen zijn de meest voorkomende psychiatrische stoornissen en de symptomen van stemmings- en angststoornissen komen ook vaak samen voor. Deze comorbiditeit tussen stemmings- en angststoornissen heeft implicaties voor de diagnostiek en voor de behandeling met antidepressiva, en vormt het onderwerp van dit proefschrift. De laatste drie decennia is er aanzienlijke vooruitgang geboekt rondom de farmacologische behandeling van stemmingstoornissen. Het effect van antidepressiva is niet beperkt gebleven tot de behandeling van stemmingsstoornissen. Patiënten met angststoornissen hebben ook baat bij behandeling met antidepressiva. Ondanks de toegenomen kennis over antidepressiva en het brede indicatiegebied is het nog altijd niet mogelijk een goede voorspelling te maken van de respons op een bepaald antidepressivum, dan wel om relevante respons verschillen tussen antidepressiva op te sporen. Behalve dat tricyclische antidepressiva (TCA) waarschijnlijk effectiever zijn bij de behandeling van ernstig depressieve patiënten, zijn er geen eenduidige verschillen gevonden tussen TCAs en selectieve serotonine heropname remmers (SSRIs) voor de behandeling van stemmings- en angststoornissen.

Hoofdstuk 1, 2 en 3 vormen een theoretische inleiding op het empirisch onderzoek dat gepresenteerd wordt in de daaropvolgende hoofdstukken. Hoofdstuk 1 is een algemene inleiding met uiteenzetting van de onderzoeksvragen. Het optreden van comorbiditeit van stemmings- en angststoornissen speelt een rol bij de interpretatie van behandelresultaten al wordt dit vaak genegeerd. Juiste classificatie van stemmings- en angststoornissen wordt bemoeilijkt door het bestaan van comorbiditeit. De diagnostische criteria van de DSM (Diagnostic and Statistical Manual of Mental Disorders) zoals geformuleerd door de American Psychiatric Association maken geen duidelijk onderscheid tussen deze patiëntengroepen ook al categoriseert de DSM stemmings- en angststoornissen als aparte groepen. De bestaande overlap van depressie- en angstsymptomen brengt ons bij de vraag of stemmings- en angststoornissen werkelijk verschillende syndromen zijn of een onderdeel vormen van een en hetzelfde syndroom. Als nu verschillende antidepressiva (bijv. TCAs en SSRIs) worden onderzocht bij zogenaamde 'pure' patiëntengroepen met een depressieve stoornis ofwel een angststoornis, blijft het de vraag of de behandelingen werkelijk even effectief zijn, zoals blijkt uit onderzoeksresultaten. In hoeverre de patiënt herstelt van slechts een stemmingsstoornis, van de bijbehorende angstsymptomen of vice versa blijft onbekend. Met andere woorden, mogelijke respons verschillen tussen antidepressiva kunnen verborgen blijven omdat patiënten selectie is gebaseerd op de DSM criteria van stemmings- en angststoornissen. De DSM is wereldwijd geaccepteerd maar classificatie op basis van de DSM heeft niet geresulteerd

in de identificatie van de juiste patiënten groepen voor behandeling met specifieke antidepressiva.

Het doel van dit onderzoek was dan ook om respons op TCAs versus SSRIs te bestuderen bij een brede groep patiënten met een stemmingsstoornis, een angststoornis of beiden. Hierdoor werd de selectie bias die optreedt bij het includeren van aparte diagnostische categorieën waarschijnlijk gereduceerd. Vervolgens zijn twee alternatieve modellen geëxploreerd voor de identificatie van subgroepen van patiënten die mogelijk verschillend reageren op antidepressiva, te weten de rol van primaire diagnose en de rol van temperament. Verder was er speciale aandacht voor het gebruik van een systematische diagnostische procedure voor de selectie van de patiënten. Dit onderzoek was dan ook gericht op twee aspecten: 1) diagnostische nauwkeurigheid van stemmings- en angststoornissen (zie Hoofdstuk 5) en 2) respons op antidepressiva (zie Hoofdstuk 6 en 7).

Hoofdstuk 2 is gericht op comorbiditeit van stemmings- en angststoornissen en de implicaties van comorbiditeit voor onderzoek. In dit proefschrift verwijst de term comorbiditeit naar de situatie waarbij meer dan een psychiatrische stoornis gediagnosticeerd wordt bij dezelfde persoon. De comorbiditeit percentages verschillen enorm tussen studies van 15% tot 91%. Deze spreiding is te wijten aan de verschillen in de definitie van comorbiditeit, steekproef selectie, tijdsduur van de studie en gekozen meet instrumenten. Verder gaat een angststoornis vaker vooraf aan een stemmingsstoornis dan omgekeerd, en angststoornissen hangen samen met een verhoogd risico op een stemmingsstoornis later in de tijd. Tot slot, als stemmings- en angststoornissen samen voorkomen, hangt dit vaak samen met hogere ernst van de klachten, een chronisch verloop, slechter behandelresultaat en een hogere incidentie van suïcide.

Hoofdstuk 3 beschrijft het persoonlijkheidsmodel van Cloninger en het model van Temperament in het bijzonder. Temperament verwijst naar de individuele verschillen in automatische reacties en gewoonten van mensen. Het model bevat vier dimensies van temperament: Novelty Seeking (sensatie zoekend), Harm Avoidance (gevaar vermijdend), Reward Dependence (belonings afhankelijk) en Persistence (volhardend). Het theoretisch model en de bijbehorende vragenlijst, de Tridimensional Personality Questionnaire (TPQ), worden nader toegelicht in Hoofdstuk 3. Het persoonlijkheidsmodel van Cloninger wordt in verband gebracht met differentiatie tussen responders en nonresponders op behandeling met antidepressiva. Ter illustratie, hoge scores op Harm Avoidance zijn gerelateerd aan een slechte response op antidepressiva. In het huidige onderzoek is het model van temperament dan ook gebruikt om respons op behandeling met een TCA dan wel een SSRI bij patiënten met stemmings- en angststoornissen te exploreren. In plaats van ons te richten op de DSM categorieën gebaseerd op huidige symptomatologie, biedt het persoonlijkheidsmodel van Cloninger een alternatieve typologie van patiënten gebaseerd op temperament.

Hoofdstuk 4 geeft een overzicht van het onderzoeksproject waarvan de resultaten in de daaropvolgende hoofdstukken zijn beschreven. Speciale aandacht is besteed aan de selectie procedures en de geanalyseerde steekproef aantallen bij de beantwoording van de verschillende onderzoeksvragen.

In Hoofdstuk 5 zijn de bevindingen rondom de diagnostische overeenstemming van stemmings- en angststoornissen beschreven. In concreto, de diagnose volgens het klinisch oordeel van de psychiater werd vergeleken met de diagnose volgens een gestructureerd diagnostisch interview bij patiënten met stemmings- en/of angststoornissen. De Munich Diagnostic Checklists (MDCL) werden gebruikt door de psychiaters om de DSM-III-R diagnose te bepalen. De psychologen namen de Composite International Diagnostic Interview (CIDI) waarmee ook de DSM-III-R diagnose werd vastgesteld. De resultaten toonden slechts matige overeenstemming tussen de klinische diagnose van stemmings- en angststoornissen en de CIDI diagnose. De overeenstemming was het grootst voor de depressieve stoornis, al betrof het slechts een matige overeenstemming. De laagste overeenstemming werd gevonden voor de gegeneraliseerde angststoornis. Verder werd gevonden dat comorbiditeit tussen stemmings- en angststoornissen vaak voorkomt volgens de CIDI terwijl de psychiaters meer geneigd zijn te kiezen voor een stemmingsstoornis dan wel een angststoornis. Deze bevinding suggereert dat clinici wellicht weinig aandacht hebben voor de bestaande comorbiditeit en laat verder zien dat er belangrijke verschillen tussen diagnosen van stemmings- en angststoornissen optreden als verschillende diagnostische procedures worden gebruikt. Dit bemoeilijkt de interpretatie van onderzoeksresultaten en de generalisatie ervan voor zowel psychologische als farmacologische behandelingen.

In Hoofdstuk 6 zijn de bevindingen beschreven over de rol van de primaire diagnose (de diagnose van de eerste ziekte episode) op de behandelrespons op antidepressiva. Er is voor een andere studieopzet gekozen dan gebruikelijk in klinisch onderzoek. Om vertekening (*bias*) te voorkomen door het bestaan van comorbiditeit zijn alle patiënten met een DSM-III-R stemmings- of angststoornis voor wie behandeling met antidepressiva is geïndiceerd geincludeerd. Response op een TCA (imipramine) of een SSRI (fluvoxamine) werd in eerste instantie onderzocht over de gehele groep (dus inclusief depressie en angst symptomen). Als uitkomstmaat is een compositie schaal gebruikt bestaande uit de depressie, angst en OCS items van de CPRS (CPRS-MA). De CPRS-MA is nog niet gevalideerd en daarom hebben we ook de Klinische Globale Impressie (CGI) gebruikt voor een algemene impressie van de verbetering onafhankelijk van specifieke symptomen. Voor de totale groep werden geen verschillen gevonden tussen behandelrespons van fluvoxamine en imipramine. Vervolgens werden de patiënten gegroepeerd op basis van hun primaire diagnose. De CIDI werd gebruikt om te bepalen of de diagnose van de eerste ziekte episode een stemmingsstoornis was (primaire depressie) of een angststoornis (primaire angst stoornis). De hypothese

dat imipramine effectiever is voor de behandeling van primaire depressie en fluvoxamine effectiever voor de behandeling van een primaire angststoornis werd ondersteund. Patiënten met primaire depressie reageerden beter op imipramine na 2 weken behandeling (maar niet na 6 weken), volgens zowel de CPRS-MA als de CGI. Patiënten met een primaire angststoornis daarentegen, reageerden beter op fluvoxamine volgens de CGI, maar niet volgens de CPRS-MA. De verschillen in resultaten tussen de CPRS-MA en de CGI werden bediscussieerd samen met beperkingen van deze studie. De resultaten veronderstellen dat informatie over de eerste ziekte episode van grotere betekenis is dan de huidige DSM classificatie van stemmings- en angststoornissen. Dit onderschrijft het belang van differentiatie tussen primaire en secundaire depressie voor de predictie van behandelrespons.

In Hoofdstuk 7 zijn de bevindingen over de rol van temperament op respons op antidepressiva beschreven. Gebaseerd op de assumptie dat temperament meer gerelateerd is aan respons op antidepressiva dan de DSM diagnose, bestond de onderzochte steekproef uit patiënten met een stemmingsstoornis, een angststoornis of beiden. De hypothese was dat patiënten met hoge Harm Avoidance scores beter reageren op fluvoxamine dan op imipramine omdat verondersteld wordt dat Harm Avoidance geassocieerd is met verhoogde kwetsbaarheid voor angst en/of serotonerge neurotransmissie. De belangrijkste bevinding was dat Harm Avoidance inderdaad was gerelateerd aan respons op antidepressiva, maar er werd geen onderscheid gevonden tussen fluvoxamine en imipramine. Een aantal methodologische kwesties werden bediscussieerd, waaronder het meten van temperament na 6 weken behandeling in plaats van voor aanvang van de behandeling. Terwijl Harm Avoidance werd verondersteld een relatief stabiele persoonlijkheidskenmerk (*trait*) te zijn, bleek het samen te hangen met huidige stemming (*state*), wat duidelijke implicaties heeft voor de interpretatie van de resultaten.

Tot slot worden in Hoofdstuk 8 de belangrijkste resultaten bediscussieerd als ook methodologische beperkingen die samenhangen met het gebruik van een nieuw paradigma om verschillen in behandelrespons op antidepressiva op te sporen. Het gebruik van de CPRS-MA als uitkomst maat, bepalen van de primaire diagnose, het meten van temperament, en selectie bias worden bediscussieerd. Het hoofdstuk eindigt met suggesties voor verder onderzoek. Dit exploratieve onderzoek betrof een eerste aanzet om respons verschillen van verschillende antidepressiva op te sporen waarbij een andere studieopzet werd gekozen dan tot dusver gebruikelijk in klinisch onderzoek. Valideren van de uitkomstmaat en replicatie van de bevindingen is dan ook nodig voordat aanbevelingen voor de klinische praktijk gedaan kunnen worden.

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Curriculum Vitae

Esther de Kemp werd op 8 december 1967 geboren te Gemert. In 1986 behaalde zij het VWO diploma aan het Macropedius College te Gemert. Hierna ging zij Gezondheidswetenschappen studeren aan de toenmalige Rijksuniversiteit Limburg te Maastricht (inmiddels Universiteit Maastricht geheten). In 1992 behaalde zij het doctoraal diploma met als afstudeerrichting Geestelijke Gezondheidkunde, nadat ze een laatste studiejaar had ingevuld met een onderzoeksstage aan de University of Illinois te Rockford USA. Ze begon haar loopbaan als research-assistent bij de RIAGG Maastricht. Daarnaast kreeg ze een aanstelling als toegevoegd onderzoeker bij de vakgroep Sociale Psychiatrie van de Universiteit Maastricht. In 1994 zij ze Maastricht vaarwel en startte een promotie onderzoek met dit proefschrift als resultaat. Van 1994 tot 1998 was zij aangesteld als Assistent in Opleiding (AiO) bij de vakgroep Klinische Psychologie en Persoonlijkheidsleer van de Katholieke Universiteit Nijmegen. Naast de AiO-baan is zij in 1994 gestart met de VGT-opleiding tot gedragstherapeut waarvoor zij op het Ambulatorium behandelingen verrichtte. Sinds 1996 is zij als gedragstherapeut i.o. werkzaam bij HSK-Groep te Nijmegen en Rosmalen. Sinds 1998 volgt zij de insteekroute tot psychotherapeut. Zij is inmiddels geregistreerd Gezondheidszorgpsycholoog en hoopt zich spoedig te kunnen registreren als gedragstherapeut en psychotherapeut.