

**Feasibility and efficacy of  
treatment for anxiety  
in primary care**

Christine van Boeijen



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**Christina Alberta van Boeijen**

The study presented in this thesis was performed at the Department of Psychiatry of the Vrije Universiteit, GGZ Buitenamstel, The Netherlands and the Institute for Research in Extramural Medicine (EMGO Institute) of the Vrije Universiteit, The Netherlands. The EMGO Institute participates in the Dutch School of Primary Care Research (CaRe), which was acknowledged in 1995 by the Royal Dutch Academy of Sciences (KNAW).

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# **Feasibility and efficacy of treatment for anxiety in primary care**

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**PART 1**

# **INTRODUCTION**

PREFACE

BACKGROUND AND RESEARCH QUESTIONS • CHAPTER 1



# Preface

## Introduction

The main subject of this thesis is the development and the testing on efficacy and feasibility of a guided self-help treatment to be used in general practice for the prevalent anxiety disorders panic disorder with or without agoraphobia (PA) and generalized anxiety disorder (GAD).

Anxiety disorders are prevalent in general practice: Ormel et al (1994) found a prevalence rate of current diagnosis of 10.4% for all anxiety disorders. In primary care, PA and GAD have life time prevalence rates of 3.8% and 2.3% (Bijl et al, 1997). Patients with anxiety disorders usually worry about their somatic health. As a consequence they frequently visit their general practitioner asking for laboratory tests, a somatic screening, and referrals to a medical specialist or simply reassurance for their worries. Since anxiety disorders often run a chronic course when untreated, they form a major burden to the health system. The large appeal these patients make upon the health system weighs heavily upon its limited capacity (Wittchen, 1988; Yonkers et al, 1996; Bijl et al, 1997). In secondary care there is considerable evidence that PA and GAD can be effectively treated with psychological treatment (Emmelkamp et al, 1995; Barlow, 2002). Therefore, it seems likely that there is a role for psychological treatments adjusted for use in primary care. Increasing availability of short effective and suitable treatments for primary care would be a welcome solution for the capacity problem.

GP's treating their anxiety disorder patients can turn to the anxiety disorder guidelines which were published in 1997 by the Dutch College of General Practitioners and revised in 2004 (Neomagus et al, 1997; Terluin et al, 2004). A problem with these guidelines is that, up till now, their efficacy was not evaluated. Some GP's find them difficult to follow in clinical practice because of the emphasis on the application of cognitive behavioural instructions, which they find rather complicated and difficult. Therefore, a self-help manual for the most prevalent

anxiety disorders was developed along the lines of the anxiety disorder guidelines. The literature shows that treatment with self-help manuals in anxiety disorder patients in primary care is effective (Bower et al, 2001). But former research also shows that dropouts are a problem in its use. Since compliance appeared to be related to a better treatment effect (Kupshik and Fisher, 1999), the format of guided self-help by the GP was chosen. Because PA and GAD are the most prevalent in general practice they became the focus of this manual.

A brief introduction of the clinical picture of PA and GAD is given in chapter 1. (In chapter 1 the research questions will also be described.) The literature on the efficacy of self-help manuals for anxiety disorders is reviewed in chapter 2. The development of the guided self-help manual and a pilot study in a small number of patients in order to establish its feasibility is subject of chapter 3. As it appeared that such a guided self-help manual is feasible and effective in primary care patients with panic disorder and generalized anxiety disorder, we compared its differential efficacy with treatment according to the anxiety disorder guidelines of the Dutch College of General Practitioners and cognitive behavioural therapy (CBT) delivered by experienced therapists. Short-term outcome of this Randomized Controlled Trial and its 6 months and 1-year follow-up is described in chapter 4. In addition, some prediction analyses were done in chapter 5.

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## Chapter 1

# Background and research questions

### Introduction

The mental disorders listed in the section 'anxiety disorders', of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, APA, 1994) are mainly characterized by severe feelings of anxiety and/or phobic avoidance behaviour. Anxiety manifests itself by feelings of apprehension, fearfulness or terror with or without a known cause. These feelings are usually associated with somatic symptoms such as: shortness of breath, palpitations, dizziness, chest pain or nausea. Patients may worry about these somatic symptoms and believe that they suffer from an undetected severe medical illness. As a consequence they frequently rely upon the health care system. The phobias are characterized by the fear of a certain object or situation which is therefore avoided or in case avoidance is impossible, endured with marked distress or anxiety. In addition, the anxiety and phobic symptoms must lead to clinically significant impairment or distress in social and occupational functioning.

In this thesis we will limit ourselves to panic disorder with or without agoraphobia (PA) and generalized anxiety disorder (GAD), as these syndromes are the anxiety disorders the general practitioner is most frequently confronted with. Moreover, both anxiety disorders can be treated in general practice. Below, a brief overview concerning these disorders is prescribed. We will go into the clinical picture, diagnosis, epidemiology, comorbidity, assessment and treatment.

## Clinical picture

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Patients with PA suffer from unexpected panic attacks, which are discrete periods of intense fear or discomfort, accompanied by physical symptoms such as palpitations, chest pain and breathlessness in addition to the fear of dying by a heart attack. After the first panic attack, patients often seek help at the first aid department of a hospital. In most cases extensive physical examination follows without an explanation for the occurrence of the panic symptoms. Other patients visit their general practitioner (GP) with complaints of avoiding travelling by public transportation and busy shops. These patients are afraid of having a panic attack at such places, and may feel depersonalized, dizzy, and are afraid to faint. Avoidance of such situations where a panic attack may occur is called agoraphobia. Most patients with panic disorder suffer from agoraphobia as well. Places which are avoided include busy shops, waiting in a cue, public transportation, travelling by car, visiting cinema, doing physical exercises, being outside the home alone and confined closed places such as elevators or toilets. When patients have company of someone they trust and who can help in case of a panic attack, the agoraphobic avoidance usually is less severe than when alone. Some people speak openly about their agoraphobic avoidance, others, however, feel ashamed and conceal their fears, as for example a house wife who is asking her husband to do all shopping in the evening for one week together, thus avoiding shopping alone and subsequently feeling 'unreal'.

Patients with GAD have as their main characteristic that they worry excessively and feel anxious about possible dangers and problems which could arise in the future. They worry for example about their health and that of their children and spouse, about their housing, finances and their job. They are afraid that they are not able to cope with these problems. Patients are not able to control their worries. They continuously feel restless, hunted, tense and nervous. The chronic worrying and anxiety are accompanied by physical symptoms including fatigue, muscle tension, dry mouth, nausea, palpitations, dizziness, diarrhoea and transpiration. Because patients have the feeling they always walk on the edge to cope with daily life, they minimize contact with others and limit their activities which they experience as most burdensome. Sometimes they try to prevent worrying by arranging an overloaded day programme, making them exhausted. Some try to check their spouse and children by calling frequently to be sure nothing bad is going on at that moment. Most patients with generalized anxiety disorder worry about worrying ('meta-worry'). They worry that they should lose their mind by worrying, that it is not normal to worry and that they are not able to control their worry.

Patients with anxiety disorders usually worry about their somatic health. As a consequence they frequently visit their general practitioner asking for laboratory tests, a somatic screening, and referrals to a medical specialist or simply reassurance for their worries. Since PA and GAD are both prevalent disorders and often run a chronic course when untreated, they form a major burden to the health system (Bijl et al, 1997; Wittchen et al, 2002). PA patients make heavy demands on primary care services (Sherbourne et al, 1996). Both anxiety disorders are associated with considerable disability and inappropriate healthcare utilisation (Katon et al, 1990; Wittchen et al, 2002). Patients with pure GAD were associated with disability, high utilization of health care resources and suicidality (Wittchen et al, 2002).

As a consequence of these anxiety disorders, patients are disabled in their social and occupational functioning. Until recently, patients with GAD were dismissed as 'worried well', implying that they there really is no burden of this disorder. However, GAD patients were found to be even more disabled than patients with panic disorder (Hoehn-Saric, 1981; Wittchen et al, 2002) while in a second study the impairment of GAD was found to be comparable with the impairment of PA (Nisita et al, 1990). The latter finding was supported by a study comparing 357 patients with GAD and/or PA (Massion et al, 1993). No significant differences were found between both disorders on suicide attempts (about 10% in both disorders), receiving disability benefit (about 25% in both disorders), receiving public assistance (about 35% in both disorders), and impaired social functioning (about 45% in both disorders).

## **DSM-IV diagnostic criteria and diagnosis**

---

Both panic attacks and agoraphobia are part of different anxiety disorders. They have no diagnostic value on their own, and can not be diagnosed as separate conditions. The criteria for panic attacks and agoraphobic avoidance, defined in the DSM-IV (APA, 1994 pages 395-397), are presented in the tables 1 and 2.

According to the DSM-IV, PA is diagnosed when panic attacks are unexpected and when at least one of the attacks has been followed by one month (or more) of persistent concern about having additional attacks, worry about the implications of the attacks or its consequences, or a significant change in behaviour related to the attacks (APA, 1994, page 402). The panic attacks are not due to the direct physiological effects of a substance (e.g., use of drug or medication) or general medical condition (e.g., hyperthyroidism). The panic attacks must not be better accounted for by another mental disorder, such as social phobia, specific,

obsessive-compulsive disorder, posttraumatic stress disorder, or separation anxiety disorder.

When a patient with PA is also extremely afraid of entering public places like shopping malls, trains, cinemas or other situations from which escape would be difficult or in which help would not be available in case of a panic attack, this person is said to have panic disorder with agoraphobia.

**Table 1: DSM-IV criteria for panic attack**

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. palpitations, pounding heart, or accelerated heart rate
2. sweating
3. trembling or shaking
4. sensations of shortness of breath or smothering
5. feeling of choking
6. chest pain or discomfort
7. nausea or abdominal distress
8. feeling dizzy, unsteady, light-headed, or faint
9. derealisation (feeling of unreality) or depersonalisation (being detached from oneself)
10. feeling of losing control or going crazy
11. fear of dying
12. paresthesias (numbness or tingling sensations)
13. shills or hot flushes

DSM-IV=diagnostic and statistical manual of mental disorders, fourth edition

**Table 2: DSM-IV criteria for panic disorder with or without agoraphobia**

- A. Both (1) and (2):  
 recurrent unexpected panic attacks  
 at least one of the attacks has been followed by one month (or more) of one (or more) of the following:  
 persistent concern about having additional attacks  
 worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")  
 a significant change in behaviour related to the attacks
- B. Presence or absence of agoraphobia (with or without agoraphobia)
- C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or general medical condition (e.g., hyperthyroidism).
- D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive-compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

DSM-IV=diagnostic and statistical manual of mental disorders, fourth edition

**Table 3: DSM-IV criteria for agoraphobia**

- 
- A. Anxiety about being in place or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situational predisposed panic attack or paniclike symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in a line; being on a bridge; and travelling in a bus, train, or automobile. Note: Consider the diagnosis of specific phobia if the avoidance is limited to one or only a few specific situations, or social phobia if the avoidance is limited to social situations.
  - B. The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a panic attack or panic like symptoms, or require the presence of a companion.
  - C. The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as social phobia (e.g., avoidance limited to social situations because of fear of embarrassment), specific phobia (e.g., avoidance limited to a single situation like elevators) obsessive-compulsive disorder (e.g., avoidance of dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., avoidance of stimuli associated with a severe stressor), or separation anxiety disorder (e.g., avoidance of leaving home or relatives).
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DSM-IV=diagnostic and statistical manual of mental disorders, fourth edition

GAD is defined as unrealistic or excessive anxiety and worry, present during at least six months. The anxiety and worry is associated with at least three physical symptoms like restlessness or feeling on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, or insomnia. The focus of the anxiety and worry is not confined to features of another Axis I disorder (e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder) gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatisation disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

**Table 4: DSM-IV criteria for generalized anxiety disorder**

- 
- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance).
- B. The person finds it difficult to control the worry.
- C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past six months).
- restlessness or feeling keyed up or on edge
  - being easily fatigued
  - difficulty concentrating or mind going blank
  - irritability
  - muscle tension
  - sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
- D. The focus of the anxiety and worry is not confined to features of an Axis I disorder (e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder) gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatisation disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.
- E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.
- 

DSM-IV=diagnostic and statistical manual of mental disorders, fourth edition

PA and GAD are diagnosed on the basis of a psychiatric interview. A medical examination may be needed to exclude the presence of physical disorders that can cause the symptoms of panic or generalized anxiety. Well-known causes of panic-like symptoms are hyperfunction of the thyroid, hypoglycemia and pheochromocytoma. The use of psychoactive substances like caffeine, cannabis or cocaine and the withdrawal from benzodiazepines or alcohol may also produce panic and anxiety. In all these situations the diagnosis PA or GAD cannot be established because of exclusion criteria in the DSM. Instead, the patient is diagnosed anxiety disorder due to a general medical condition with panic attacks/general anxiety or substance-induced anxiety disorder with panic attacks/generalized anxiety.

## Epidemiology

In Table 5 the prevalence in primary care of PA (lifetime 3.8%) and GAD (lifetime 2.3%) are presented as found in the Netherlands NEMESIS study (Bijl et al, 1997). These data confirm earlier American research (Regier et al, 1988) indicating that these anxiety disorders are prevalent in the general population. PA and GAD are more common in females than in males. In contrast to GAD, PA has an acute onset, with the occurrence of the first unexpected panic attack. The peak prevalence lies in the third decade of life. GAD develops gradually with a mean age of 23 years (Thyer et al, 1985). Untreated, PA and GAD run a chronic course with a waxing and waning of symptoms (Wittchen 1988; Yonkers et al, 1996).

Table 5: prevalence of PA and GAD from the Netherlands 'NEMESIS' study in percent by DSM III R criteria in general practice, and prevalence of PA from the American 'E.C.A.' study in percent by DSM III criteria in general population

	'NEMESIS' study		'E.C.A.' study
	prevalence PA (%)	prevalence GAD (%)	prevalence PA (%)
1-month	1.5 (0.1)	0.8 (0.1)	0.5 (0.1)
6-months	2.2 (0.2)	1.2 (0.1)	0.8 (0.1)
life-time	3.8 (0.2)	2.3 (0.2)	1.6 (0.1)

NEMESIS=Netherlands Mental Health Survey and Incidence Study. DSM-III-R= diagnostic and statistical manual of mental disorders, third revised edition. ECA=Epidemiologic Catchment Area. DSM-III = diagnostic and statistical manual of mental disorders. PA=panic disorder. GAD=generalized anxiety disorder.

## Diagnosis in secondary and primary care

A reliable way of diagnosing PA and GAD is the use of the Structural Clinical Interview for Psychiatric Disorders (SCID-IV; First et al, 1997). In this structured interview patients are systematically inquired about the presences of the DSM-IV criteria of the disorders. The main advantage is high reliability and validity of this measurement. Disadvantage, however, is the duration of the SCID, which may last up to one and half hour. With the SCID an overall kappa was found of .85 (0.06), range = .71-.97, being an excellent level of agreement (Ventura et al, 1998).

However, the SCID is too time consuming for use in primary care. An alternative reliable way of diagnosing PA and GAD in primary care is the use of the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spitzer et al, 1994). With the PRIME-MD an overall kappa was found of .71. PRIME-MD was developed as a screening instrument but its administration time has limited its clinical usefulness. A self-administered PRIME-MD Patient Health Questionnaire (PHQ) has been developed. This self-report questionnaire (PHQ) has comparable diagnostic

validity to the PRIME-MD, and is more efficient to use in primary care settings. With the PHQ an overall kappa was found of .65 (Spitzer et al, 1999).

## **Recognition of GAD and PA in primary care**

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It appears that the GP recognizes less than half of psychological problems (Ormel et al, 1991; Satorius et al, 1993). These studies demonstrated that physician recognition of anxiety disorders is poorer than that of depression in primary care settings. One study suggested that PA patients were more likely to be missed in primary care when patients are known with other medical illnesses (Roy-Byrne et al, 2000a). Another explanation of poor recognition may be due to a weak presentation of the anxiety symptoms by the patients. Particularly, when patients demonstrated physical type of symptoms recognition of anxiety disorders will be more difficult. Sometimes general practitioners interpret the presented symptoms for example as a consequence of the personality structure of the patient (Jenner et al, 1995).

It has long been noticed that the majority of mental illnesses seen in community surveys have not been referred to the mental health services. There is a filtering process at work between the community and the mental health in-patient treatment. The framework consisted of five levels: 1) community; 2) primary care (total); 3) primary care (identified); 4) Mental illness services (total); and 5) Mental illness services (in-patients) (Goldberg & Huxley, 1992). In our study we will focus on primary care-identified patients.

## **Comorbidity**

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PA and GAD appear to be frequently comorbid with other anxiety disorders, mood disorders and substance related disorders. In early clinical research high comorbidity levels for especially GAD were found. This led to the suggestion of GAD to be a 'severity marker' of other syndromes rather than a separate disorder. However, later studies in the general population showed that the proportion of comorbid disorders in GAD was about as large as in other disorders. Apparently, comorbidity in GAD is associated with help-seeking behaviour (Wittchen et al, 1994).

In addition, in the Wittchen et al (1994) study it was found that in 9.6% of the cases GAD was the only disorder diagnosed, indicating that GAD is indeed an independent disorder. Another 12,2% reported that the age of onset of GAD was

earlier than that of any other comorbid disorder. Together, these patients with primary GAD make up approximately one fifth (21.8%) of all GAD cases. This was confirmed by Maier et al (2000), who found that in about 25% of the cases in general practice GAD is the only disorder present.

In table 6 comorbidity patterns for PA and PAD, derived from the 'NEMESIS' study are presented (Ravelli et al, 1998). The clinical relevance of diagnosing these disorders with or without comorbid disorders is concerned with the fact that patients with comorbid disorders are more severely and chronically ill, more disabled, utilize services more frequently and are more difficult to treat (Angst & Vollrath, 1991; Roy-Byrne et al, 2000b). However targeted CBT for panic disorder has beneficial effects on comorbidity over the longer term (Tsao et al, 2005).

Table 6: Co-morbidity in panic disorder and generalized anxiety disorder from The Netherlands 'NEMESIS' study in percent (%) by DSM-III-R criteria.

	PA	Agorafobie	Specific phobia	Social phobia	OCD	GAD
PA	-	-*	12	17	34	23
GAD	26	21	11	17	25	-

NEMESIS=Netherlands Mental Health Survey and Incidence Study. DSM-III-R= diagnostic and statistical manual of mental disorders, third revised edition. PA=panic disorder. GAD=generalized anxiety disorder. OCD=obsessive compulsive disorder. All associations are significant. \*= $n < 5$

## Treatment

In secondary care there is considerable evidence that PA and GAD both are effectively treated with pharmacological and psychotherapeutic treatments (Emmelkamp et al, 1995; Barlow, 2002). Although there are some differences between the treatments for PA and GAD, we limit ourselves to the similarities. Pharmacological treatment consists mainly of antidepressants, while effective psychotherapeutic interventions comprise cognitive-behavioural treatment (CBT). These treatments improve anxiety symptoms, panic attacks, worry and avoidance behaviour.

The major body of research has been done in patients with PA. In the short-term, antidepressants and CBT are comparably effective for patients with panic disorder without agoraphobia. However, in case patients suffer from agoraphobic avoidance behaviour as well, the combination of antidepressants with exposure in vivo is superior to antidepressants and CBT alone (Van Balkom et al, 1997). In the long-term, these treatments remain effective, and the combination treatment remains superior over its elements (Bakker et al, 1998). Up till now, in GAD, no comparisons have been made between antidepressants and CBT. The limited

research into long-term outcome indicates that treatments remain effective. Rates of quality care for anxiety disorders are moderate to low in university-affiliated primary care practices. Although an appropriate type of pharmacotherapy was frequently used, it was often of inadequate duration. CBT was markedly underused. These findings emphasize the need for practice guidelines and implementation of quality improvement programs for anxiety disorders in primary care (Stein et al, 2004).

The Dutch College of General Practitioners has recently updated the anxiety disorder guidelines (Neomagus et al, 1997; Terluin et al, 2004). As these guidelines are evaluated in the main study of this thesis, we describe them briefly below. Next, we discuss CBT in more detail, and finish with the developed self-help manual for PA and GAD which is also tested in the main study.

### **Anxiety disorder guidelines by the Dutch College of General Practitioners**

In 1989 the Dutch College of General Practitioners (NHG) [Nederlands Huisartsen Genootschap] published their first practice guideline. This guideline, which was concerned with the treatment of Diabetes Mellitus type II in the general practitioner's practice, marked the beginning of a success story. Now, 13 years later, more than 75 guidelines have made their debut and the guidelines hold an integral place in all initial General Practitioner education programme in The Netherlands. It is estimated that the published guidelines cover approximately 60% of the problems seen in the daily practice. The anxiety disorder guidelines belong to this series of guidelines with the aim to improve and support an evidence-based general practice of these disorders (Neomagus et al, 1997; Terluin et al, 2004). Up till now, the efficacy of the anxiety disorder guidelines has not been evaluated yet. The anxiety disorder guidelines pertain to recognition, diagnosis and treatment of 6 anxiety disorders. We limit ourselves here to the treatment section.

According to the guidelines treatment starts with extensive information on the diagnosed anxiety disorder. The GP informs the patient about the relation of the somatic symptoms he experiences and PA/GAD. When needed, a somatic screening can be used to reassure the patient that the symptoms experienced are no sign of an underlying somatic disease. The diagnoses 'PA' and/or 'GAD' are explicitly named, so that patients know which disorder they suffer from. The GP reviews with the patient possible causes for the anxiety symptoms, in order to

identify factors which induce and maintain panic attacks, anxiety, worry and avoidance behaviour.

Treatment is aimed at the reduction of anxiety symptoms to a level which is acceptable for the patient. First, the GP makes a inventory of possible psychosocial stressors and the use of psychotropic substances related to anxiety. The use of caffeine, alcohol and marihuana should be normalised or minimised in order to decrease anxiety symptoms. The GP informs the patient about the role of catastrophic cognitions and avoidance behaviour in the maintenance of anxiety symptoms. When needed the GP can give the patient simple exposure in vivo instructions or exercises, or ask the patient to register his anxiety-related cognitions in a diary.

The anxiety disorder guidelines leave the GP free to refer the patient to a psychiatric outpatient clinic, to refer to a physiotherapist for relaxation exercises, or to prescribe benzodiazepines, antidepressants and buspirone for GAD.

### **Cognitive-behavioural therapy**

Below we discuss CBT for PA and GAD separately. In the main treatment study, we used two treatment protocols: one for PA and one for GAD. The protocols were highly overlapping and in case of comorbidity the interventions were combined.

The treatment of PA is largely based on the model of Clark (1986), which has proven to be effective in the treatment of PA. Treatment starts with the explanation of the model of panic disorder and the rationale of the treatment. The vicious circle for panic is explained and automatic catastrophic cognitions are identified. In the next step these automatic cognitions are challenged by means of the Socratic dialogue. A hyperventilation provocation test may be done to demonstrate the overlap of bodily symptoms with a panic attack. It may also be used as a first step in challenging the catastrophic misinterpretations of bodily symptoms. In the next sessions more catastrophic cognitions are challenged and replaced by more realistic and rational cognitions. The patient has to challenge these cognitions at home. To strengthen the evidence that the catastrophic way in which the somatic symptoms were interpreted is incorrect, behavioural experiments were added. Finally, an individual hierarchy is made of situations avoided. To overcome the avoidance behaviour, exposure in vivo exercises may be added.

Treatment of GAD is based on its cognitive behavioural models developed (Borkovec & Inz, 1990; Clark, 1989; Wells, 1997/2002) and found effective by Durham & Turvey (1987), Butler et al (1991), Borkovec & Costello (1993) en

Durham et al (1994). Treatment starts with an explanation of this model, emphasizing the crucial role of catastrophic and 'meta' cognitions. The patients' individual catastrophic cognitions are identified and challenged also with the aid of behavioural experiments. Subsequently, alternative and more realistic cognitions are formulated. An applied relaxation training is given. Patients systematically learn to relax in anxiety provoking situations with the use of an audiotape (Öst, 1987). Avoidance behaviour and safety behaviour is identified and placed in an individual hierarchy and treated with exposure in vivo and response prevention exercises.

### **Guided self-help treatment**

Since self-help manuals based on cognitive and behavioural principles are relatively easy to administer and do not require large time investments by the general practitioner, they may be used in the treatment of anxiety disorders in primary care. Up till now, these self-help manuals have been developed and tested mainly in mental health specialist care settings (Greist et al, 1986; Gosh et al, 1988). Recently, however, several effectiveness studies have been published on self-help treatment in primary care patients with anxiety disorders (Milne & Covitz 1988; Donnan et al, 1990; Sorby et al, 1991; White, 1995; Kupshik & Fisher, 1999; Sharp et al, 2000). Overall, they appear to be somewhat less effective than therapist delivered intensive treatments (Tyrer et al, 1988; Gould & Clum, 1993; Sharp et al, 2000). Follow-up data suggest that the treatment gains of self-help interventions sustain from 12 months to 3 years (Gould & Clum, 1993; Lidren et al, 1994; White, 1998). The major problem of the use of self-help manuals is that of lesser patient compliance and the tendency to drop out when difficulties occur in the application of the manual (Kupshik and Fisher, 1999). To overcome this problem, in this thesis, a guided self-help manual was developed, including several contacts with the GP who supports and encourages the patient to continue with the manual.

The self-help manual studied was written under supervision of two experienced cognitive behaviour therapists. Material was used of English booklets with contains information in self-help for patients with panic disorder, avoidance and generalized anxiety disorder (Butler, 1985, Fennell & Butler, 1985 and Sorby et al, 1991) and a part of the booklet developed for social phobia with exercises of applied relaxation by Öst (1987) (Beek, 1996). The self-help manual comprises an introduction, education about anxiety, cognitive techniques, relaxation exercises and exposure in vivo. The patient is advised to spread the treatment over 12 weeks. At the end of each chapter the patient can answer self-control questions. In addition, the patient is advised not to carry out the treatment alone, but instead call

in the help of a friend or relative. When the ‘helper’ is asked, the patient can present him the flyer with information about the treatment. Added to the manual were an audiotape with relaxation exercises, a registration book, an exercise book and a book with the answers to the questions in the manual.

## Research Questions

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The main object of the studies in this thesis pertains to the relative efficacy of guided self-help treatment, CBT and anxiety disorder guidelines of the Dutch College of General Practitioners in primary care patients with PA and GAD in the short-term and long-term. A review, a pilot of the Guided Self-Help Treatment and some issues on the prediction of treatment outcome were studied as well.

Up till now, several effectiveness studies have been published on self-help treatment in primary care patients with anxiety disorders. These studies compared self-help with waiting lists or with care as usual in primary care or with CBT in secondary care. In reviewing these studies systematically, we want to give an overview of the present knowledge of the effectiveness and the feasibility of treatment with self-help manuals for the anxiety disorders in primary care. This review is presented in Chapter 2.

In Chapter 3 a pilot study is described on the effectiveness and feasibility of the developed guided self-help program in five selected primary care patients with PA and/or GAD. The content of the self-help manual will be discussed in detail. Outcome was assessed with validated measurement instruments which were filled out directly before the start with the self-help manual and 12 weeks later.

In Chapter 4 a 12-week RCT with a 12 and 40 week follow-up period is described comparing the relative efficacy of guided self-help treatment, CBT and the anxiety disorder guidelines of the Dutch College of General Practitioners. General Practitioners were randomised to the two conditions delivered in general practice. CBT was delivered by experienced cognitive behavioural therapists in a psychiatric outpatient clinic specialised in the treatment of anxiety disorders. Primary care patients who met DSM-IV criteria for panic disorder and/or generalized anxiety disorder were randomly assigned to receive treatment in primary care or 12 sessions of CBT. The primary outcome measure was the Spielberger State-Trait Anxiety Inventory – state subscale (STAI-state: Spielberger et al, 1970). Secondary outcome assessments included well-validated scales measuring other psychiatric symptoms and associated features of these disorders. Since the three treatments differed mainly in the intensity and complexity of the cognitive behaviour

techniques used, we hypothesised that the most intensive form (CBT in secondary care) would give the best results, followed by manual and with guidelines as a significantly poorer third.

In Chapter 5 a study of the influence of type of comorbidity on the 1-year course of a sample of 141 outpatients with panic disorder with or without agoraphobia and generalized anxiety disorder receiving different forms of cognitive behaviour therapy. This was determined on change scores (linear regression analysis) and remission data (Kaplan-Meier survival analysis). Three categories as assessed at pretest were compared: no comorbidity, comorbidity among anxiety disorders and comorbidity with mood disorders. Primary outcome variable: State-Trait Anxiety Inventory State subscale measured at four assessments (0, 12, 24 and 52 weeks).

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# **PRELIMINARY STUDIES**

**A SYSTEMATIC REVIEW • CHAPTER 2**

Efficacy of self-help manuals for anxiety disorders  
in primary care: a systematic review

**AN ANALYSIS IN SINGLE CASES • CHAPTER 3**

Treatment of panic disorder and/or generalized  
anxiety disorder with a guided self-help manual:  
an analysis in single cases



## Chapter 2

# A systematic review

## Efficacy of self-help manuals for anxiety disorders in primary care, a systematic review

This chapter was published:

van Boeijen CA, van Balkom AJLM, van Oppen P, Blankenstein N, Cherpanath A, van Dyck R (2005). Efficacy of self-help manuals for anxiety disorders in primary care, a systematic review. *Family Practice* 22(2):192-196.

### Abstract

#### Objective

To review effectiveness studies of self-help manuals for anxiety disorders in primary care.

#### Methods

A systematic review of six identified randomized controlled trials. In addition to outcome the articles were coded on quality variables.

#### Results

The studies included differed with respect to the methodological quality, measurements used and size of the study population. Despite these differences, global results suggest that a self-help manual is an effective treatment possibility for primary care patients with anxiety disorders. The more time was spent to the guidance of the self-help manual the higher its effectiveness was.

## Conclusions

Treatment with a self-help manual for anxiety disorders may be effective in primary care. Data are lacking on the feasibility and cost-effectiveness of these manuals.

## Keywords

Systematic review, anxiety disorders, primary care, self-help manual

## Introduction

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General practitioners (GPs) play an important role in the treatment of patients with anxiety disorders because these disorders are highly prevalent in general practice (10-20%), (Ormel et al, 1994; Bijl et al, 1997) and these patients can not always be treated adequately in secondary care settings due to a limited capacity. As only a small number of patients with anxiety disorders remits spontaneously, an adequate treatment is necessary for most patients. The GP usually treats anxiety disorders with either benzodiazepines or antidepressants. Albeit effective, these drugs may have several disadvantages such as the occurrence of undesirable side effects, relapse after discontinuation and the risk of dependency. These disadvantages may lead to a poor patient compliance and a relatively high dropout rate. In contrast, the effectiveness and tolerability of cognitive behavioural therapy (CBT) with a small tendency to relapse after treatment has repeatedly been demonstrated in the short-term and long-term. Unfortunately it is difficult to deliver CBT adequately in primary care, because it requires an extensive training of the therapist and should be delivered on a weekly basis in ten to twenty sessions of 45 to 60 minutes. It has been attempted to modify CBT into a more efficient, cost-effective, and affordable treatment (Bond & Dryden, 2002). One of these modifications comprises the use of self-help manuals. Since such manuals are relatively easy to administer and do not require large time investments, they may be used in the treatment of anxiety disorders in primary care.

Up till now, several effectiveness studies have been published on this subject (Bower et al, 2001; Newman et al, 2003). We want to review these studies systematically on the effectiveness and the feasibility of treatment with self-help manuals for the anxiety disorders in primary care, to identify gaps of knowledge and suggest future research.

## Methods

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### Inclusion criteria

We included randomised-controlled trials (RCT) evaluating the effectiveness of self-help manuals in the treatment of anxiety disorders in primary care. Self-help manuals were defined as booklets or manuals aimed to overcome anxiety disorders and designed to be used by the patient himself or in conjunction with limited therapist contact. We were especially interested in panic disorder (PD) and generalized anxiety disorder (GAD) because these disorders are highly prevalent in primary care. Studies with a mixed population, i.e. anxious and depressed patients, were excluded when data on the sub-sample with anxiety disorders was not separately provided. In an attempt to identify all studies, the quality of the study was not used as an exclusion criterion.

An initial search of the Pub Med, PsycLit/PsycInfo and Cochrane database was done for the period 1963 to June 2003, using the keywords 'anxiety disorders', 'PD', or 'GAD' in combination with 'self-help', 'general practice', 'primary care' or 'family practice'. This search was extended by a manual search of the cross-references from the included papers.

### Data extraction

CAvB and AJLMvB independently reviewed the studies selected by filling out a coding form. After the studies were coded twice, discrepancies in the two coding forms were resolved by referring to the data of the original article. This method yielded one coding form per article. The coding form consisted of the following items: year of publication, sample size, diagnosis, diagnostic criteria, duration of disorder, age, sex, intervention type, duration of intervention, presence and duration of follow-up and global results at posttest and at follow-up. Moreover, the methodological quality of the studies included was assessed with the Amsterdam-Maastricht consensus list, range 0-19 points (Van Tulder et al, 1997).

### Analysis

In order to get an impression of the magnitude of the results obtained after treatment with a self-help manual, effect sizes Cohen's *d* were calculated on anxiety outcome measures. The effect size was calculated within interventions by subtracting posttest from pretest scores and dividing the difference by the pooled standard deviation (Hunter & Schmidt, 1990).

As follows below, it appeared that the studies included differed with respect to the methodological quality, the measurements used and the size of the study population. Therefore, we decided not to pool the results. Due to the small number of studies included, no formal statistical analyses were used, with exception of some non-parametric correlations.

## Results

The initial search yielded a total of 966 reference titles in Pub Med, 293 in PsycLit/PsycInfo and five in Cochrane database. After screening abstracts or full text of the articles found, four studies and one follow up study were identified on the effectiveness of self-help manuals in the treatment of anxiety disorders in primary care. A manual search of the cross-references of the articles found, yielded two other papers of possible relevance. After reading the full text, six studies and one follow up study could be included in this review (see Table 1).

Table 1: **Reasons why papers were not included**

Database	PubMed (n)	PsycLit/Info (n)	Cochrane (n)
Initial search	966	293	5
Excluded on abstract/ full text	963	291	5
No anxiety disorders	299	38	0
Anxiety disorders mixed with other diagnosis	44	2	0
No primary care	36	21	0
No self-help manual (videotape/ computer)	10	9	0
Review/overview	166	34	1
Treatment outcome study	146	64	3
Epidemiology/prevalention study	33	9	0
Diagnostic study	158	57	0
Prediction outcome study	21	14	0
Medical utilization in anxiety disorders	14	6	0
Other (mainly letters/editorials/ books)	36	37	1
Included studies & follow up study	3*	2**	0

\* Sorby (1991); Kupshik (1999); Sharp (2000)

\*\* reference White (1995); White (1998)

Handsearch reference Milne (1988); Donnan (1990)

Table 2 shows scores on the methodological quality of the included studies measured with the Amsterdam-Maastricht-consensus list. Due to the type of the intervention investigated, in none of the studies the care provider and the patients were blind. Moreover, in none of the studies adverse effects were provided.

Therefore, the maximum quality score of the studies selected was 16. The quality of the studies ranged from moderate (Donnan et al, 1990; Kupshik & Fisher, 1999) to good (Sharp et al, 2000). Recency of the study correlated moderately with better quality (Spearman's rank correlation: 0.41;  $p=0.42$ ).

Table 2: **Validity scores of included studies by two independent reviewers measured with the Amsterdam-Maastricht consensus list**

Authors (year of publication)	Milne & Covitz (1988)	Donnan et al (1990)	Sorby et al (1991)	White (1995)	Kupshik & Fisher (1999)	Sharp et al (2000)
<b>Validity criteria</b>						
Adequate randomisation procedure	+	+	+	+	+	+
Concealed random allocation of treatments	0	-	-	0	-	+
Pretest similarity tested	-	+	+	+	+	+
Control for co-interventions in design	+	-	-	-	-	+
Check for adherence to interventions	+	-	+	+	+	+
Valid outcome measure	+	+	+	+	+	+
Relevant outcome measure	+	+	+	+	+	+
Outcome assessor blinded	0	-	-	-	-	+
Care provider blinded	-	-	-	-	-	-
Patient blinded	-	-	-	-	-	-
Withdrawals and drop-outs (proportion; inequality between groups; reasons for withdrawal/drop-out reported)	+	-	+	+	-	+
Identical timing of outcome assessment for all intervention groups	+	+	+	+	+	+
Intention-to-treat analysis	-	-	-	-	-	+
<b>Descriptive criteria</b>						
Specification of eligibility criteria	-	-	+	+	0	+
Description of the interventions	+	+	+	+	-	+
Follow-up	+	-	-	+	+	-
Adverse effects	-	-	-	-	-	-
<b>Statistical criteria</b>						
Sample size: to be presented at randomisation and outcome	+	+	+	+	+	+
Presentations of point estimates and distribution measures	+	+	+	+	-	+
<b>Total score (range 0-19)</b>	<b>11</b>	<b>8</b>	<b>11</b>	<b>12</b>	<b>8</b>	<b>15</b>

+ present, - absent, 0 not provided

Table 3: Characteristics and outcome of the included studies

Authors Publication year	Study population (n)	Diagnosis	Diagnostic criteria	Mean duration of anxiety problem	Drop outs	Age (years) Mean Range	Sex
Milne & Covitz 1988	22	Anxiety	-	-	18% 4/22 1 month	Mean 53 Range 20-67	13F 5M
Donnan et al 1990	103	Anxiety	-	-	38% 39/103 3 months	Median 42 Range 17-77	75F 26M
Sorby et al 1991	64	PD GAD Phobic avoidance	DSM III	>1 months 4.1% 1-3 months 14.3% 4-6 months 6.1% >6 months 75.5%	23% 15/64 8 weeks	Range > 18	52F 12M
White 1995	97	Anxiety disorder	DSMIII-R	3.2 yr 2.8 yr 2.4 yr	0% 0/97 3 months	Mean 38.3 Range 18-65	36F 26M
Kupshik & Fisher 1999	102	Anxiety	Zung Anxiety Scale	36,4 months (range 1 month to 10 years)	22% 22/102 1.5 months	Mean 38.8	43F 37M
Sharp et al 2000	104	PD ± A	DSM III-R	(1) 26.8 months (2) 44.3 months (3) 38.2 months	24% 25/104 3 months	Mean 38.3 Range 18-70	-

PD=panic disorder. A=agoraphobia. GAD=generalized anxiety disorder. DSM=Diagnostic and Statistical Manual of Mental Disorders. F=female. M=male. CBT=cognitive behaviour therapy. "-"=unknown or not present. "\*" = reference White 1998.

Table 3: Characteristics and outcome of the included studies

Authors Publication year	Intervention Number of patients per intervention (n)	Duration of intervention	Global result at post test	Duration of follow-up	Global result at follow-up
Milne & Covitz 1988	(i) manual (7) (ii) a health education leaflet (5) (iii) waiting list control group (6)	1 month	1=2=3	6 months	1=2=3
Donnan et al 1990	(i) manual (51) (ii) care as usual (52)	3 months	1=2	-	-
Sorby et al 1991	(i) manual (30) (ii) care as usual (19)	2 months	1>2	-	-
White 1995	(i) manual (21) (ii) advice only (20) (iii) waiting list (21) and after three months all CBT	3 months	1>2=3	3 years*	1>2=3
Kupshik & Fisher 1999	(i) manual and minimal contact (29) (ii) manual and medium contact (23) (iii) manual and maximum contact (28)	1.5 months	1<3 1=2 2=3	3 months	1>3 1=2 2=3
Sharp et al 2000	(i) manual (29) (ii) manual and 2 hours CBT(31) (iii) manual and 6 hours CBT (31)	3 months	1<2=3	-	-

Characteristics and outcome of the included studies are shown in Table 3. As follows from Table 3, the six studies included differed on the diagnosis included, the diagnostic criteria used, the duration of the intervention (range 1-3 months), presence of a follow-up period (in three of six studies) and duration of the follow-up (range 3 months - 3 years). Overall, the study sample was rather small and the dropout rate relatively high. In four studies the self-help manual was compared to control conditions as a waiting list or care as usual (Milne & Covitz, 1988; Donnan et al, 1990; Sorby et al, 1991; White, 1995; White, 1998). Two studies did not find significant differences between respectively the manual versus a waiting list (Milne & Covitz, 1988) and the manual versus care as usual (Donnan et al, 1990). In contrast, the other two studies showed superior outcome of the self-help manual. One negative study used a very small sample (each condition included less than ten patients) (Milne & Covitz, 1988), while the other negative study had only a moderate by large quality score (Donnan et al, 1990).

Two studies compared the self-help manual with other interventions, characterised by increasing guidance or hours of contact (Kupshik & Fisher, 1999; Sharp et al, 2000). The global results suggest that the more contact the patient received the higher the effect of the manual was (see later). It is noteworthy that a self-help manual was even effective in a sample of patients with a duration of anxiety complaints of more than one year. The small number of follow-up data suggest, that the treatment gains of self-help manuals are sustained until after 12 months and 3 years (White, 1995; White, 1998).

In three studies effect sizes could be calculated on anxiety measures. These are shown in Table 4. The effect sizes Cohen's *d* associated with treatment with a manual only varied from 0.38 to 1.74. This large difference is due to the type of measurement used and the duration of the study (one month seems rather short to overcome anxiety symptoms). In corroboration with global outcome, the magnitude of the effect sizes was critically dependent of the additional time spent to the guidance of the manual (Spearman's rank correlation: 0.85;  $p=0.004$ ).

Table 4: Effect sizes of the interventions of the included studies

Authors publication year	Interventions Number of patients per intervention (n)	Outcome measures	
		STAI (state)	STAI (trait)
Milne & Covitz 1988	(i) manual (7)	0.38	0.03
	(ii) a health education leaflet (5)	0.13	0.15
	(iii) WL (6)	-0.07	0.15
		SCL-90 total	HADS anxiety
White 1995	(i) manual (21)	1.08	1.74
	(ii) advice only (20)	0.05	0.56
	(iii) WL (21)	0.24	0.26
		GSS	
Sharp et al 2000	(i) manual (29)	0.53	
	(ii) manual and 2 hours CBT (31)	1.29	
	(iii) manual and 6 hours CBT (31)	1.92	

SCL-90=symptom checklist 90. HADS=Hospital anxiety and depression scale. STAI=state-trait anxiety inventory. GSS=Global symptom severity. CBT=cognitive behaviour therapy. WL=waiting list

## Discussion

We can conclude that treatment with a self-help manual for anxiety disorders in primary care may be effective. The magnitude of the effect size Cohen's *d* for this treatment varied from moderate to large. Moreover, it was found that the more time was spent to the guiding of the self-help manual the higher its effectiveness was. Even patients with longstanding anxiety symptoms may profit from treatment with a self-help manual. None of the studies reported on the feasibility in primary care practice.

The conclusions of the present study are limited, because we could only include six studies on this subject. These studies differed with respect to quality, measurements and study size and are therefore difficult to compare. Although some of the studies only had a moderate quality, validated questionnaires were used, making comparison possible with the literature. In a recent meta-analysis CBT provided in secondary care for panic and agoraphobia was associated with an effect size of 1.25 respectively 0.91 (White, 1998). Most effect sizes of this review are somewhat smaller, corroborating with the observation that the more time spent to the guiding of the manual the better outcome was.

Future research should focus on the treatment of well-defined anxiety disorders in general practice, the feasibility of using a (guided) self-help manual in this setting and the cost-effectiveness especially compared with second-line CBT.

General practice is an environment of limited resources which aims to provide the time and attention a patient needs, but not more. If spontaneous recovery does not occur in anxiety disorder patients in primary care, a minimal intervention in the form of a self-help treatment may be offered. The results of this study may fit in a stepped care approach and suggest that (guided) self-help manual may be a first line treatment of anxiety problems in primary care.

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## Chapter 3

# An analysis in single cases

## Treatment of panic disorder and/or generalized anxiety disorder with a guided self-help manual: an analysis in single cases

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### Abstract

The aim of this pilot study was to test the effectiveness and feasibility of a new guided self-help program in five selected primary care patients with panic disorder (PD) and/or generalized anxiety disorder (GAD). Most patients achieved a clinically relevant improvement after 12 weeks of treatment with large effect sizes Cohens'  $d$  on all measures. Two patients could be considered as recovered according to the criteria of Jacobson and Truax. Although all patients appeared to be improved on all outcome measures, PD was more easy to treat than GAD. These results suggest that a guided self-help manual treatment is an effective treatment possibility in the treatment of PD and GAD in primary care. When these results can be replicated in a controlled trial in a larger sample, guided self-help treatment may be a first line treatment in general practice in a stepped care approach of PD and GAD.

### Key words

Self-help manual, Panic Disorder, Generalized Anxiety Disorder and primary care.

## Theoretical and research basis

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General practitioners (GPs) play an important role in the treatment of patients with anxiety disorders because these disorders are highly prevalent in general practice. The prevalence of anxiety patients in primary care medical setting has been estimated to range between 5% and 20% (Ormel et al, 1994; Sartorius et al, 1993; Spitzer et al, 1995; Bijl et al, 1997). All these patients can not be treated adequately in secondary care settings due to capacity limits. The GP usually treats anxiety disorders with either benzodiazepines or antidepressants. Albeit effective, these drugs may have several disadvantages such as the occurrence of undesirable side effects, relapse after discontinuation, and the risk of dependency. These disadvantages may lead to a poor patient compliance and a relatively high dropout rate. In contrast, the effectiveness and tolerability of cognitive behavioural therapy (CBT) has repeatedly been demonstrated in the short-term and long-term, with a small tendency to relapse after treatment. Unfortunately it is difficult to deliver CBT adequately in primary care, because it requires an extensive training of the therapist, and should be delivered on a weekly basis in ten to twenty sessions of 45 to 60 minutes. To overcome these disadvantages treatment researchers have recently attempted to make CBT more efficient, cost-effective, and affordable (Bond & Dryden, 2002). One approach for enhancing efficiency is to make use of self-help manuals.

Since self-help manuals based on cognitive and behavioural principles are relatively easy to administer and do not require large time investments from the GPs, they may be used in the treatment of anxiety disorders in primary care. Up till now, these self-help manuals have been tested mainly in mental health specialist care settings. Overall, they appear to be somewhat less effective than therapist delivered intensive treatments (Tyrer et al, 1988, Sharp et al, 2000). Follow-up data suggest that the treatment gains of self-help interventions were sustained even after 12 months (White, 1995; van Balkom et al, 2000). Major problems in the feasibility of self-help manuals are the tendency for patients to have a low compliance and to stop the use of the manual when difficulties occur. To overcome these problems, we applied *guided* self-help: this includes some contacts with the GP who supports and encourages the patient to continue with the manual.

There is a clear need to investigate the effectiveness of these treatment programs in primary care (Beek, 1996). The aim of this pilot study was to test the effectiveness and feasibility of a new guided self-help program for primary care patients with panic disorder (PD) and generalized anxiety disorder (GAD).

## Cases introduction

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Patient 1 is a 46-year-old married Caucasian female. She was living with her husband and 17-year old daughter. Her 24 years-old son lived on his own. After finishing primary school she became a housewife.

Patient 2 is a 49-year-old divorced, homosexual Caucasian male. Once married he found out he had homosexual feelings, leading to a divorce. After finishing high school he worked as an illustrator.

Patient 3 is a 39-year-old single Caucasian female. After finishing high school she worked freelance as a marketing researcher.

Patient 4 is a 60-year-old divorced Caucasian female, living with her son. After primary school she started working for one day a week as a housekeeper and was a housewife.

Patient 5 is a 63-year-old widowed female, whose husband died 10 years ago. She has two daughters, 37 and 31 years old. After primary school she went to a school for domestic economy. She did not graduate, but started working in home care.

## Presenting complaints

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Patient 1 was diagnosed with Panic Disorder (PD) with agoraphobia and dysthymic disorder. When she started treatment with the self-help manual, she suffered from panic attacks for 8 years. During these attacks she experienced palpitations, shortness of breath, dizziness, fear of losing self-control and fear of dying. She was afraid of having a panic attack in places like elevators, stairs, toilets or a queue. She avoided places from where she could not escape easily, such as supermarkets, theatres, children's playgrounds and airplanes. She also avoided public transportation, walking alone in the street, going far away from home alone and thinking of illnesses or accidents. For others, she tried conceal her anxiousness when she experienced bodily symptoms like palpitations and breathlessness.

Patient 2 presented with a diagnosis of PD with agoraphobia and co-morbid hypochondriasis and dysthymic disorder. After his divorce, he started with drinking alcohol in large amounts. Two years ago he suddenly experienced unusual bodily feelings like shaking and a dry mouth. He was afraid of having a heart attack. At that moment he was alone in a crowded place buying alcohol in a shop. From there, he called the emergency department. As he was told that alcohol could induce panic symptoms, he stopped the drinking of alcohol completely.

However, he remained anxious and lost his job. From then on, he suffered from unexpected panic attacks with symptoms of breathlessness, chest pain, stomach pain, dizziness, depersonalisation, paresthesias and fear of doing something uncontrolled, to faint or to die from a heart attack. He avoided situations from which he could not leave easily, like the soccer stadium and crowded places, and was afraid to sport. He was also afraid to die of aids or long cancer in spite of reassurance by a physician, and felt depressed most time of the day, with sleeping problems, poor concentration and feeling helpless. He took 5 mg of oxazepam per day, and smoked marihuana on a daily basis to feel more relaxed.

Patient 3 was diagnosed with PD with agoraphobia and dysthymic disorder. She suffered from unexpected panic attacks for 8 years with palpitations, sweating, paresthesias, dizziness, shortness of breath, chest pain, nausea, feeling unreal, getting warm and cold, fear to loose control or to die of a heart attack or by choking. She avoided going out to crowded places like cafes and shops, going alone far from home, and small closed places like elevators, busses and airplanes.

Patient 4 presented with PD with agoraphobia, GAD, social phobia, posttraumatic stress disorder and dysthymic disorder. She suffered from unexpected panic attacks, with complaints of palpitations, sweating, paresthesias, shortness of breath, feeling dizzy and fear to loose control, and avoided situations such as going out alone, visiting a birthday, going to church, traveling by bus, train or driving a car, being in a supermarket, waiting in a line. From childhood onwards, she suffered from excessive worrying most of the day. Recent topics were her children, finances, and the health of her mother. These symptoms were complicated 18 years ago with a panic attack when she was home, lying on the couch. Upset about these symptoms, she called the primary care physician who gave her medication to calm down.

Patient 5 was diagnosed with GAD, PD partly in remission and hypochondriasis. She was worried that something bad could happen to her children and felt restless and irritated. She suffered from tense muscles. Due to her fear of having cancer, she avoided to attend preventive breast examination. Many bodily symptoms were interpreted as the evidence of having cancer. She had panic attacks with symptoms of palpitations, breathlessness, pain in the chest, stomach pain, dizziness, feeling unreal, paresthesias, feeling hot and cold, and was afraid to die.

## History

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Patient 1 experienced her first panic attack at night in bed when she was thinking about her son who was on vacation alone and became afraid that he was lost. She became anxious, had smothering sensations and paresthesias and was afraid to faint. The agoraphobic avoidance started after a panic attack while driving on a highway one year later. From now on, her anxiety and avoidance increased and she became depressed as well, suffering from insomnia, overeating, and having low energy, low self-esteem, poor concentration and feelings of hopelessness. Since two years she used daily 75mg of clomipramine (an antidepressant), to which she responded only partially. She drank 12 glasses of wine as self-medication weekly.

Patient 2 received former treatment with hypnosis, psychotherapy on analytic lines and fluvoxamine (an antidepressant). These treatment did not affect his anxiety symptoms. Since fluvoxamine had appeared ineffective, he had stopped this antidepressant.

Patient 3 underwent his first panic attack immediately after the use of marihuana. Due to her symptoms, she became insecure and depressed most of the time with complaints of poor appetite, sleeplessness, fatigue, low self-esteem, concentration difficulties and feeling helpless. Prior to the self-help treatment she received physiotherapy for half a year, with only a small effect on these symptoms.

Patient 4 had panic attacks every day. After a divorce all her complaints worsened thirteen years ago. She avoided to go out alone, to travel with public transport or to visit crowded places like churches, supermarkets, birthday parties and weddings. After school she became anxious to perform in front of strangers. More and more she was afraid of scrutiny by others. Feeling depressed most of the time, she also suffered from sleeplessness, fatigue, and a low self-esteem. During her marriage her husband assaulted her several times, leading to a post traumatic stress disorder. She relived these traumas over and over again and avoided situations resembling the assaults. She felt strange and empty as if she was not there, and complained of being more irritable, of difficulty concentrating and of being hypervigilant. She used 30 mg oxazepam daily for 11 years.

Patient 5 started having panic attacks 15 years ago after the death of her husband who suffered from a myocardial infarction, multiple sclerosis, lung emphysema and bladder cancer. The panic attacks were complicated with worries, when eleven years ago her sister and mother died of cancer and her daughter had a baby who died at birth. Fifteen years ago she was prescribed oxazepam and haloperidol (an antipsychotic drug) by a psychiatrist for one year. She saw a psychologist for 4 years.

## Assessment

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The patients filled out self-report measurements at 0 and 12 weeks. All measures are validated for The Netherlands and show good psychometric properties.

(1) General Health Questionnaire (GHQ-12; Goldberg & Williams, 1988). This questionnaire of 12 items is a reliable and valid rating scale to assess an overall self-rated measure of well being (range: 0-12). According to the formulas developed by Jacobson and Truax (1991) the reliable change score on the GHQ-12 is a change of more than 3 points. The recovery criterion on the GHQ-12 is a posttest score of less than 3. (Koeter & Ormel, 1991; Piccinelli et al, 1993; Van Hemert et al, 1995).

(2) Fear Questionnaire (FQ; Marks & Mathews; 1979). This questionnaire, consisting of 20 items, is a reliable and valid rating scale to assess severity of avoidance of several phobic situations (range: 0-160). According to Jacobson and Truax (1991) on the FQ total phobia and anxiety/depression subscales the reliable change was a score of at least 23 points respectively 11 points. The recovery criterion on the FQ subscales differs by sex. Recovered females must score less than 32 and males 33 on the FQ total phobia subscale. For the FQ anxiety depression subscale a score of 13 for females and 14 for males was required (Marks and Mathews, 1979; Arrindell et al, 1984; Mizes & Crawford, 1986).

(3) Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch & Lushene, 1970).

This self-report questionnaire measures reliable and valid the presence and severity of general anxiety with 20 anxiety state and 20 anxiety trait items (range: 20-80, Van der Ploeg, 1980).

(4) Lehrer-Woolfolk Anxiety Symptom Questionnaire (LWASQ; Lehrer & Woolfolk, 1982).

This 36-item questionnaire is a reliable and valid measurement of severity of somatic, cognitive and behavioural aspects of anxiety (range: 36-180; Scholing & Emmelkamp, 1992).

## **Case conceptualization**

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For this pilot study, three GPs were asked to screen patients visiting their practice on a probable anxiety disorder with the short and simple screening interview of Goldberg et al (1988). When patients were able and willing to travel to our outpatient clinic and probably wanted to work on their problems with a self-help manual with guidance from a medical doctor, the GPs made an appointment for their patient. With the Dutch version of the Anxiety Disorder Interview Schedule (ADIS IV; Di Nardo et al, 1983) a trained medical doctor supervised by a psychiatrist, diagnosed patients with a main diagnosis of PD and/or GAD according to the DSM-IV (APA, 1994). Moreover, patients were excluded using more than 30mg oxazepam daily. In the case patient used other benzodiazepines the dosage of this benzodiazepine was converted to the equivalent doses of oxazepam. We included patients with these main disorders only, because the self-help manual focuses primarily on these disorders. However, included patients were allowed to have secondary diagnoses as for example dysthymic disorder or other anxiety disorders. We did not include patients who had received cognitive or behavioural treatment in the past, because the self-help treatment used cognitive-behavioural elements. Patients were allowed to take psychopharmacological drugs, provided by their GP's, when dosages were kept constant during the self-help treatment. Five patients were included and completed treatment with the self-help manual (one male, four females; mean age 51.4 years, range 39-63 years; mean duration of complaints 9.2 years, range 21 months to 15 years; three patients with PD, two patients with co-morbid GAD and PD).

## **Course of treatment: the self-help manual**

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The first author wrote the self-help manual with supervision of two experienced cognitive behaviour therapists. The self-help manual was discussed with the patient in 5 sessions in the course of 12 weeks. To be feasible in general practice, each session should not last more than 20 minutes. All patients were treated individually. The patients were instructed not to change the doses of benzodiazepines or antidepressants during these 12 weeks.

In the first session information was given about the treatment with the self-help manual. All patients received the self-help manual, a registration book, an exercise book, and a relaxation tape with exercises of applied relaxation by Öst and a flyer with information for a helper. They were told to reserve enough time for the treatment and to practice every week for at least three hours, throughout the week.

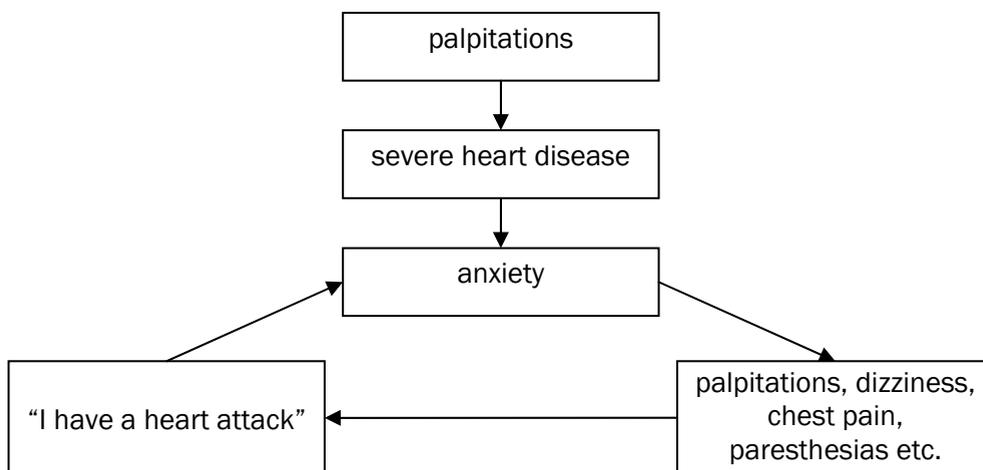
In the following four sessions the patients were asked whether they had questions about the part of the manual they worked on and whether they had carried out their homework as instructed. The therapist reinforced achievements and tried to motivate the patient to take enough time to practice and do homework. In case the patient could not follow the schedule, the therapist tried to solve this problem together with the patient. In the fifth and last session follow-up treatment was discussed.

The self-help manual comprises an introduction, information about anxiety, cognitive techniques, relaxation exercises and exposure in vivo (Fennell & Butler, 1985; Butler, 1985; Beek, 1996). At the end of each chapter the patient is asked to answer self-control questions. In the introduction, the goal of the treatment to overcome anxiety problems in 12 weeks is described. In the first chapter the manual explains how to spread the exercises over 12 weeks. In addition, the patient is advised not to carry out the treatment alone, but with the help of a friend or relative. For the 'helper' the flyer is available with information about the course of treatment and information about how to help the patient, such as assist in doing the exercises and evaluate exercises afterwards. In difficult periods the helper can motivate the patient to continue treatment. The patient is instructed to choose someone whom he trusts and who is both firm and patient. The patient is instructed to write down every day the time spent with the treatment in a registration manual.

In the second chapter information is given about normal and pathological anxiety and the consequences of the latter (bodily sensations, fear of fear, avoidance, loss of confidence). Anxiety can be interpreted as a consequence of catastrophic misinterpretations of bodily sensations. These bodily sensations are mainly those involved in normal anxiety responses. For example when a person has palpitations he can misinterpret this as a dangerous heart disease. This may result in fear of a heart attack, which is perceived as a threat. The apprehension increases and a wide range of bodily sensations like shortness of breath, sweating, and dizziness accompanies this state. If these anxiety-produced sensations are again interpreted in a catastrophic fashion, a further increase in apprehension occurs. This produces a further increase in bodily sensations and results in a vicious circle, which was

culminate in a panic attack. Other thoughts, which may enhance anxiety feelings, are 'It is very sure that things will go wrong', 'I cannot work out this problem', 'I will faint when everybody is there'. In figure 1 a panic attack according to a cognitive perspective is described, based on a figure in Clark (1986) and Wells (2002).

Figure 1: an example of a panic attack according to a cognitive perspective, based on a figure in Clark (1986) and Wells (2002)



In the third chapter a cognitive approach (situation → feelings → thoughts →) is described to identify anxious thoughts combined with ways to find alternatives. Patients can log their own anxious thoughts in a file. Some examples are provided of negative unrealistic automatic thoughts in panic and worrying. Like 'when I have palpitations, I will die of a heart attack'; 'When I feel dizzy, I will faint'; 'When I have a headache, this is a sign of a brain tumor'; 'When my friend is not coming home on time, he will have a car accident'. By describing the situations they face while having these feelings of discomfort, some underlying anxious thoughts can be identified. For example: Sitting on the couch, watching an exciting film having palpitations → anxiety → 'I have a heart attack'. Or: waiting for a husband to come home at 6 o'clock and it is now 5 minutes later → 'He is in a car accident' → anxiety. By writing this down patients can find a connection between situations, thoughts and feelings. That is a first step towards changing these unrealistic automatic thoughts. Examples of more realistic thoughts of the before mentioned examples are provided, such as 'When I have palpitations it could be due to the exciting film I am watching', or 'When my husband is home later than expected, it could be due to traffic jam'. In addition, more information about

anxiety is provided in a question and answer fashion. 'Can I do something about my anxiety problem, even if I was born this way' is answered with 'It is possible that you are more sensitive to having this anxiety problem than other people have. This does not mean that you cannot learn to deal with the anxiety at all'. In this way, the patient can see if his thoughts are as realistic as he thinks. If he is able to change and replace his dysfunctional thoughts by more functional ones his fear will decrease.

In chapter four applied relaxation is introduced. The relaxation training by tape starts with progressive relaxation with tension-release of the muscles (step 1). The short version (release-only) is introduced by step 2 and cue-controlled (conditioned) relaxation is introduced by step 3. Differential relaxation is introduced by step 4. The patients are taught rapid relaxation and practice their relaxation skills in stressful but non-panic situations by step 5. In step 6 application training in naturalistic situations is introduced (Öst, 1987). In addition, the patient learns to apply breath control techniques.

In the last chapter the patient starts with gradual exposure in vivo, by drawing up a list of avoided situations. From this list the patient constructs a fear hierarchy. He gradually exposes himself to the fearful situations with or without the helper. The patient regains confidence by actually doing these things and learning that anxiety will go away by practicing over and over again. In the exercise book, every situation which is practiced, can be scored with the amount of tension the patient feels before, during and after the practice. When a goal is reached, the patient has to repeat the exercise, after which he can start with a more difficult exercise. This part ends with encouragement to continue exposure and regaining self-confidence, by thinking positively about the things that went well. Next, the patient is advised to start doing enjoyable things in life. Finally a summary is given of the principles that the manual is based upon as well as tips on how to deal with anxiety in the future.

## Assessment of progress

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Table 1 shows the patients' scores on the questionnaires and the effect size of the 5 patients taken together. The effect size Cohen's *d* (Cohen, 1988) is calculated by dividing the difference of pretest and posttest by the mean standard deviation. The effect sizes indicated a large treatment effect on all measures.

In addition, the progress of the sample was expressed by the clinical significance of improvement (Jacobson & Truax, 1991). To fulfil this criterion: (i) a reliable change

must have been taken place, and (ii) the posttest score must meet the criterion for 'recovered'. Of the measurements used in this pilot study, we chose the GHQ-12 and the FQ subscales 'total phobia' and 'anxiety/depression' to demonstrate a 'reliable change' for each patient separately. The GHQ-12 is an instrument much used in primary care research in anxiety and depressive problems and the FQ is very sensitive for change in anxiety problems. From table 2 it follows that 2 patients could be considered recovered when measured with the GHQ-12 and the FQ anxiety/depression subscale and 4 with the FQ total phobia subscale. The patients 2 and 3 were considered recovered on all three measurement instruments.

Table 1: Outcome measures at pretest and posttest

Diagnose ▶	PD	PD	PD	PD + GAD	GAD +PD	Mean (SD)	Effect size (d)
Sex ▶	F	M	F	F	F		
Patient number ▶	1	2	3	4	5		
Questionnaire ▼							
GHQ-12							
Pretest	1	10	12	7	0	6(5,34)	1,35
Posttest	0	2	0	4	0	1,2(1,79)	
FQ total phobia							
Pretest	48	34	47	66	22	43,4(16,52)	2,36
Posttest	20	14	13	26	14	17,4(5,55)	
FQ anxiety/ depression							
Pretest	15	36	29	18	16	22,8(9,26)	1,44
Posttest	11	10	5	22	10	11,6(6,27)	
STAI state							
Pretest	53	52	55	41	52	50,6(5,5)	1,26
Posttest	48	46	46	31	43	42,8(6,8)	
LWASQ							
Pretest	98	106	130	136	97	113,4(18,35)	2,52
Posttest	63	73	59	96	69	72(14,46)	

PD=panic disorder. GAD=generalized anxiety disorder. F=female. M=male. SD=standard deviation. LWASQ=Lehrer-Woolfolk Anxiety Symptom Questionnaire. STAI=Spielberger State-Trait Anxiety Inventory. FQ=fear questionnaire. GHQ=general health questionnaire.

Figure 2: Results at pretest and posttest on the general health questionnaire (GHQ)

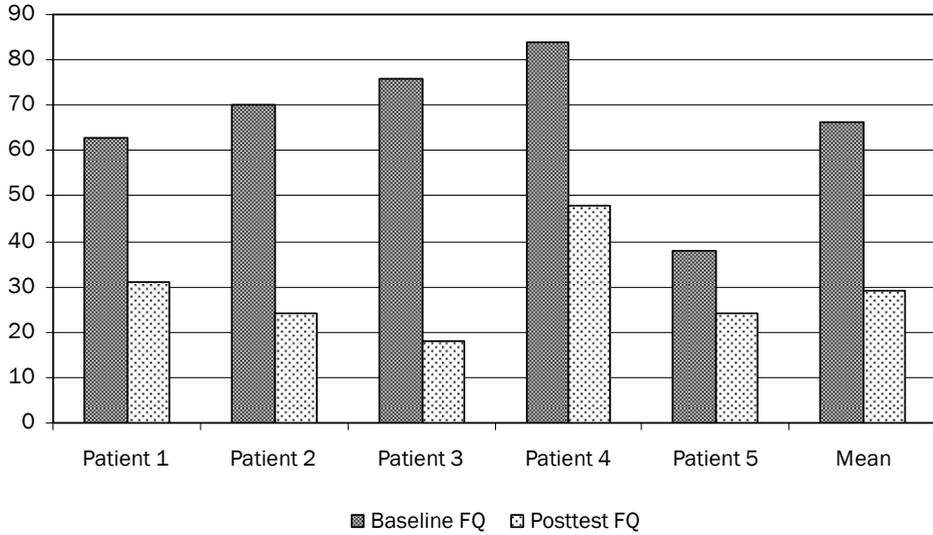
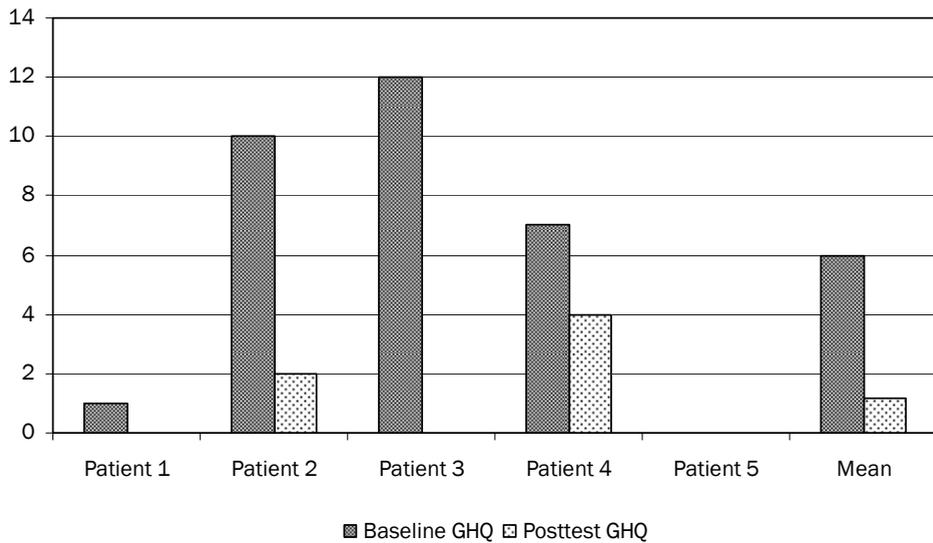


Figure 3: Results at pretest and posttest of the fear questionnaire (FQ)



All but one patient spent the advised time in doing their homework. The mean time spent by the patient at home was 2 hours and 48 minutes a week. The mean time spent per session by the therapist was 23 minutes.

Patient 1 has been seen six times in 16 weeks. After 7 weeks she felt very restless and could not concentrate. She worried about her father. She was used to care for others, especially her father, and had difficulties taking care of herself. She thought she was not capable to participate in the treatment well enough, so she decided to stop to work with the manual before the fourth session. In this session the therapist convinced her to continue, and she started again with the manual. The therapist gave her the opportunity to call between appointments when things did not work out well. She did not have the need to use this possibility. After 12 weeks (the fifth session) she felt much better, and did not have panic attacks anymore. She made a start with the exposure in vivo exercises and asked for an extra session four weeks later. During this period, in which she exercised a lot, she improved most. She gave herself a present to celebrate her successes. In the course of these 16 weeks, her self-confidence improved and she regained freedom of movement she had missed due to her fears. The agoraphobic avoidance behaviour was almost completely disappeared and she worries no longer about illnesses or accidents anymore. In general, her anxiety was diminished and she had less physical complaints such as palpitations or breathlessness. She felt no longer obliged to hide her feelings for other people. The depressive complaints diminished as well and she planned to go to her GP to taper down her clomipramine. The questionnaires showed a marked improvement of complaints. She did not meet the criteria for an anxiety disorder anymore. Especially on the phobia scale her complaints almost completely disappeared.

Patient 2 was seen five times in the scheduled 12 weeks. During treatment using the self-help manual and relaxation exercises his physical complaints diminished. He reported that he understood more about his anxiety, which gave him reassurance. The relaxation exercises helped him to feel less tense, while the exposure exercises helped him doing more what he wanted. The avoidance behaviour decreased, as did many depressive symptoms. For this patient one meeting every four weeks was not enough to continue the self-help treatment. He decided he needed more intensive treatment and planned to visit his general practitioner for a referral to a psychotherapist.

Patient 3 had 5 appointments from which it appeared that she spent quite a lot of time on her homework. Especially, she carried out the exposure tasks very well. For example, she had a vacation to Spain for 3 weeks after 6 weeks of treatment.

When she returned she reported she could travel by airplane without fear and had a nice and busy time. The panic attacks had not disappeared, but she could understand them better and accept them with less fear.

Patient 4 From the scheduled five sessions it appeared that she tried to do her homework well. However, she had difficulties with fully understanding the self-help manual. This was discussed during the sessions. She was able to carry out the relaxation exercises without problems. She had asked her daughter to help her with the exercises. In the last weeks of the treatment her daughter was absent and she stopped the exposure sessions. She mainly did the relaxation exercises, which helped somewhat. After 12 weeks, when her daughter was present again, she decided to continue the use of the manual. As table 2 shows, she markedly improved and fully recovered on the phobia scale of the FQ. Her depressive complaints remained. There was no improvement on the anxiety/depression scale of the FQ. She improved on the GHQ, which means that she felt better in life now than prior to the treatment. Her physical complaints and worries decreased.

Patient 5 was seen four times in the 12-week period. She did not have any panic attacks during treatment and explained that she benefited most from the tape with relaxation exercises. She did not want to confront her hypochondriacal fears by reading about cancer or watching medical programs, because in her opinion her complaints were not that troublesome at that moment. This fits with her rather low pretest scores (see table 2). As expected she decided not to continue using the manual afterwards.

Table 2: **Clinical significance**

Questionnaire►	General Health Questionnaire-12 conventional score		Fear Questionnaire total phobia		Fear Questionnaire anxiety-depression	
	Improved	Recovered	Improved	Recovered	Improved	Recovered
Patient number▼						
1	N	N	Y	Y	N	N
2	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y
4	Y	N	Y	Y	N	N
5	N	N	N	N	N	N

Y=yes. N=no.

## Complicating factors

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The feasibility and effectiveness of the self-help manual for general practice patients with anxiety disorders appeared to be excellent. Only few complicating factors occurred during treatment. As the complaints of patient five were not very pronounced during the twelve weeks of treatment, she decided not to do the exposure exercises. Patient four became more anxious while reading the manual. In the opinion of patient two, the guidance was insufficient. Patients 2 and 3 chose not to find a helper, because they were ashamed of having a mental disorder. These patients followed the manual on their own. In order to profit from the treatment all patients had to do much homework. This means that they must be well motivated to work on their problems. Sometimes this did not succeed (patient 5). For some patients (2 and 4) the 12 weeks of treatment was too short to profit sufficiently. They went on with psychotherapy after finishing the self-help manual.

An important weakness of this study is that the first author was the only therapist. She was quite familiar with the treatment of anxiety disorders and enthusiastic about this form of treatment. We can not rule out that her competence and her enthusiasm have influenced the effectiveness of this self-help manual in a positive way. Further testing of the self-help manual in general practitioners is needed to allow more definitive conclusions of its effectiveness.

## Managed care considerations

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The results of this pilot study suggest that a guided self-help manual treatment for PD and/or GAD is an effective treatment option in primary care. The therapist support of the manual involved 5 sessions of about 20 minutes, making it feasible in general practice as well. Most patients achieved a clinically relevant improvement. When these results can be confirmed in a controlled trial in a larger sample, guided self-help treatment may evolve into a very relevant option in general practice as part of a stepped care approach of PD and GAD. The GP should consider self-help format as an option for patients presenting with problems of PD or GAD in primary care, especially when they have preference to learn to their problems and not to choose directly for medication. In addition, it must be taken into account that patients are good candidates for treatment with the manual when they are motivated to work by their selves on these problems. In these cases self-help treatment with guidance is a valuable option to consider before starting medication or referring the patient to secondary care.

## Follow-up

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We do not have follow-up data of these patients. Since the anxiety disorders run a chronic course, long-term effectiveness of a treatment is even more important than its short-term effectiveness. A study on the long-term improvement in a larger sample is being conducted.

## Treatment implications of the cases

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These cases are examples of the effectiveness of guided self-help treatment in primary care patients with relatively severe long-standing panic disorder or GAD. However, for patients with PD the manual was more effective than for patients with GAD. This may be due to the fact that in the evaluated self-help manual no attention was paid to the change of meta-worries, frequently present in GAD (Wells, 1999).

Our treatment results may be influenced by the fact that all patients included were motivated to participate, shown by the fact that they were willing to travel to an outpatient clinic for a diagnostic interview and receive treatment with the self-help manual. In addition, the therapist (first author) was highly motivated as well to succeed in this treatment, and enhancing treatment effect of the manual. Until now there are a number of controlled studies which support the use of self-help manual for the treatment of PD, but there is less evidence for the usefulness of self-help treatment in the treatment of GAD (Milne & Covitz, 1988; Donnan et al, 1990; Sorby et al, 1991; White, 1995; Kupshik & Fisher, 1999).

The effect sizes for improvement on the anxiety measures were large and higher than reported before. Other studies with self-help manuals in primary care patients demonstrated heterogeneous effect sizes between  $-0.18$  and  $0.99$  on anxiety symptoms (Milne & Covitz, 1988; Donnan et al, 1990; Sorby et al 1991; White, 1995; Kupshik & Fisher, 1999). Perhaps the difference in the magnitude of these effect sizes is to be explained by the time spent on the treatment manual by patients and therapist. In comparison with other studies more time was spent by therapist and patient to the self-help manual. Another important difference with the above-mentioned studies is that our study was not a randomized controlled study. All patients were directly referred to the self-help manual treatment by the GP. Due to this selection it may be possible that only highly motivated patients were included.

## Recommendations to clinicians and students

In an environment of limited resources it makes sense to provide all the time and attention a patient needs, but not more. If spontaneous recovery does not occur in PD and GAD patients in primary care, a minimal intervention in the form of a self-help treatment can be offered. Especially when patients prefer psychological instead of pharmacological treatment for their anxiety symptoms this self-help manual treatment may be an alternative to referral to secondary care. In a recent study with depressed primary care patients it was demonstrated that a substantial percentage of patients preferred psychotherapy over pharmacological treatment. Patients with strong preferences, mostly for psychotherapy, are likely not to enter antidepressant treatment or randomized clinical trials if their preferences are not supported (van Schaik et al, 2004) Evidently, the use of self-help material has clear advantages. Although this preferences for psychotherapy has never been demonstrated in the treatment of anxiety disorders it is plausible that such preferences also exist in other common mental disorders.

Increased cost-effectiveness can make an effective treatment accessible to more patients in need of assistance. However, patients must be able and willing to spend time to their homework in order to be able to profit from the treatment offered. The results of this pilot study may fit in a stepped care approach and suggest that guided self-help treatment may be a first line treatment of PD and to a lesser extent GAD in general practice.

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# **MAIN STUDIES**

A RANDOMISED CONTROLLED TRIAL • CHAPTER 4  
Treatment of anxiety disorders in primary care  
practice: a controlled study.

COMORBID DEPRESSION PREDICTS OUTCOME • CHAPTER 5  
Comorbidity depression but not comorbid anxiety  
disorders predict poor outcome in anxiety  
disorders.



## Chapter 4

# A randomised controlled trial

## Treatment of anxiety disorders in primary care practice: a randomised controlled trial

This chapter was published:

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### Abstract

#### Background

Anxiety disorders are prevalent in primary care. Psychological treatment is effective but time-consuming, and there are waiting lists for secondary care. Interest has therefore grown in developing guidelines for treatment that would be feasible in primary care.

#### Aim

To compare the effectiveness and feasibility of guided self-help, the Anxiety Disorder Guidelines of the Dutch College of General Practitioners and cognitive behavioural therapy (CBT).

#### Design of study

Randomised controlled study lasting 12 weeks with follow-up at 3 and 9 months for primary care patients with panic disorder and/or generalized anxiety disorder.

**Setting**

The first two forms of treatment were carried out by 46 general practitioners (GPs) who were randomly assigned to one or the other form. CBT was carried out by cognitive behaviour therapists in a psychiatric outpatient clinic.

**Methods**

Participants (n=154) were randomly assigned to one of the three forms of treatment. The main outcome measure used was the state subscale of the Spielberger Anxiety Inventory.

**Results**

All three forms of treatment gave significant improvement between pretest and posttest, and this improvement remained stable between posttest and the follow-ups. The results obtained with the three treatment forms did not differ significantly over time. The feasibility of the Anxiety Disorder Guidelines was low compared with that of guided self-help.

**Conclusions**

Our results indicate that primary care patients with prevalent anxiety disorders for whom the GP does not find referral necessary can be adequately treated by the GP. Referral to psychiatric outpatient clinic does not give superior results. Guided self-help is easier for the GP to carry out than a less highly structured treatment like that laid down in the Anxiety Disorder Guidelines.

**Keywords**

Generalized anxiety disorder, panic disorder, randomised controlled trial, primary care, cognitive behaviour therapy, self-help treatment.

## Introduction

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The World Health Organisation study on psychological problems in general health care demonstrated a 10.1% prevalence rate for anxiety disorders (Ormel et al, 1994). As a consequence, general practitioners (GPs) often see these disorders in their patients. The most common forms are panic disorder with or without agoraphobia and generalized anxiety disorder (Bijl et al, 1997). GPs often treat anxiety disorders with antidepressants or benzodiazepines. These drugs are effective but have several disadvantages including the risk of dependency, side-effects and poor patient compliance. Furthermore, anxiety symptoms often recur when the drugs are discontinued (Rickels & Rynn, 2002; Simon et al, 2002). These disadvantages are irrelevant in treatment programs based upon cognitive and behavioural principles<sup>7</sup>. However, such programs are usually not suitable for primary care because they are time-consuming and require extensive training of the therapist. Most research into the efficacy of cognitive behavioural therapy (CBT) has taken place in secondary care settings (van Balkom et al, 1997; Bakker et al, 1998; Gorman, 2002).

In order to stimulate the use of simple cognitive behavioural techniques in primary care, the Dutch College of General Practitioners recently developed guidelines for the treatment of anxiety disorders. The efficacy and feasibility of these guidelines have not yet been evaluated (Terluin et al, 2004).

Another development in the treatment of anxiety disorders in primary care is the use of self-help manuals based on cognitive behavioural techniques. Self-help treatment appears to be effective in both the short and the long term (Bond & Dryden, 2002). However, the interpretation of these results has so far been hampered by small patient samples and the failure to use appropriate diagnostic criteria for the anxiety disorders studied (Bower et al, 2001; van Boeijen et al, 2005). In addition, the effectiveness of self-help manuals for anxiety disorders in primary care has not been compared with that of CBT in secondary care, which may be considered the gold standard in this field.

The purpose of this study is to compare the effectiveness and feasibility of a self-help manual for anxiety disorders used by the patient under the direction of the GP (referred to from now on as Manual) with CBT carried out by experienced cognitive behaviour therapists in secondary care. These two forms of treatment were further compared with the Anxiety Disorders Guidelines of the Dutch College of General Practitioners (referred to henceforth as Guidelines). Since the three treatments differed mainly in the intensity and complexity of the cognitive

behaviour techniques used, we hypothesised that the most intensive form (CBT in secondary care) would give the best results, followed by Manual and with Guidelines as a significantly poorer third.

## Methods

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### Design

The effectiveness of the three treatments for panic disorder and generalized anxiety disorder was compared in a 12-week study with a 12-week treatment-free follow-up period. After that the patients were given conventional treatment tailored to their needs. Follow-up 1 was scheduled 24 weeks after pretest, and follow-up 2 was 52 weeks after pretest. The patients were randomly assigned to the three forms of treatment: (i) use of the Manual under the guidance of the GP, (ii) CBT, given in a psychiatric outpatient clinic by experienced cognitive behavioural therapists, and (iii) Guidelines implemented by the GP. The study was approved by the Medical Ethics committee of the VU University Medical Centre and was performed from February 1998 to May 2002.

### Subjects and recruitment

The participants, all over 18 years of age, were recruited from 46 general practices in rural and urban areas of the Netherlands. GPs identified possible panic disorder or generalized anxiety disorder with the aid of the Short and Simple Screening interview (SSI, Goldberg et al, 1988). If the SSI score was 5 or more, participants were invited for a diagnostic interview using the Structured Clinical Interview technique described in DSM-IV (the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, SCID-IV, First et al, 1997). The participants were asked to participate in the study when the results of this interview showed that they met the criteria for panic disorder or generalized anxiety disorder. Exclusion criteria were the presence of an organic mental disorder; mental retardation or a psychotic disorder; treatment of anxiety disorders in the recent past; use of antidepressants or the use of more than 30mg oxazepam equivalents daily. After a full explanation of the study procedures, participants gave written informed consent.

### Sample size and randomisation

The participating practices (n=46) were first randomly assigned in a ratio of 1:1 to Manual or Guidelines as primary care method (van der Feltz & Adèr, 2000). Next,

within each practice, patients were randomly assigned to primary or secondary care in a ratio of 2:1. For both randomisations a computerised randomisation scheme was used. In both randomisation procedures (primary care practices and participants) the assignments were put in sequentially numbered sealed, opaque envelopes by an independent statistician. At the start of the study the first author opened the envelopes for the participating practices. During the study the first author opened the envelopes after participants had given their informed consent.

Our aim was to find a medium effect size (corresponding with a 5.5 point difference) on the state subscale of the Spielberger State-Trait Anxiety Inventory (STAI) between the treatment conditions. This effect size required a sample size ( $\alpha = 0.05$ ; two sided  $\beta = 0.20$ ) of 50 participants in each group. This estimated effect size was corrected for the difference between the two follow-up measurements (within-person correlation assumed to be 0.7) and the variation within GP groups (within-GP correlation assumed to be 0.2), using an assumed standard deviation of 10 (Diggle et al, 1994; Goldstein, 1995).

It was found during the study that the practices randomly assigned to Manual had on average twice as many patients as those assigned to Guidelines. As a consequence, there was an unintended difference in size between the three study groups. Having consulted an independent statistician, the authors therefore decided halfway through the study to change the primary care : secondary care randomisation ratio in the practices offering Manual from 2:1 to 1:2. Since this change could yield biased results because the equivalence of the treatment and control groups is relaxed, we analysed post-hoc whether the differences in inclusion and outcome before and after the change in the randomisation ratio critically affected our results. This did not appear to be the case. We did not find significant pretest differences in demographic and clinical status variables, nor posttest differences in outcome.

## **Treatment**

All participants received individual treatment for 12 weeks based on cognitive-behavioural principles. The three treatments differed mainly in intensity and complexity. GPs and therapists received relevant training. The GPs were present at two educational meetings on diagnosis and treatment of anxiety disorders. Supervision was provided by the first three authors every 2 months during the study. The cognitive behavioural therapists, all with extensive experience in the treatment of anxiety disorders received weekly supervision of the fourth author.

Self-help treatment consisted of five 20-minute sessions. In the first session, the GP informed the participant about the contents of the manual, which comprised an explanation of the basic facts about anxiety, simple cognitive techniques, and relaxation and in vivo exposure exercises. The participants put the self-help techniques learnt from the manual into practice for 3 hours a week. In subsequent sessions, the GP reinforced the patient's achievements and motivated him or her to continue with the use of the manual (van Boeijen et al, in press 2006).

CBT comprised twelve 45-minute sessions. The participants practiced for 3 hours a week. They received a CBT handbook explaining the basic facts about anxiety and the rationale of CBT, identifying anxiety-provoking cognitions and showing the patient how he or she can challenge these cognitions by means of a Socratic dialogue and replace them by more realistic and rational cognitions. The credibility of catastrophic cognitions was tested with the aid of behavioural experiments, and in vivo exposure exercises were given (Öst, 1987; Clark, 1989; Wells, 1997).

Guidelines was the least structured form of treatment, and consisted of a very simple form of CBT. The GP was free to choose the number of sessions and the type of intervention, but was advised to start with explanation about the nature of anxiety followed by reassurance, simple cognitive techniques and in vivo exposure. The GP was allowed to refer the patient for relaxation exercises or psychiatric treatment and to prescribe antidepressants or benzodiazepines (Terluin et al, 2004).

## Measurements

Participants filled out questionnaires at four points in time during the study, to provide a measure of the presence and severity of psychopathological symptoms associated with panic disorder or generalized anxiety disorder: pretest (immediately after informed consent had been given), posttest after 12 weeks, follow-up 1 after 24 weeks and follow-up 2 after 52 weeks.

Since the severity of anxiety is the psychopathological parameter most widely used in the diagnosis of panic disorder and generalized anxiety disorder, the state subscale of the STAI was used to determine the primary outcome measure (Spielberger et al, 1970). The following secondary outcome measures were: the trait subscale of the STAI and the Lehrer-Woolfolk Anxiety Symptom Questionnaire (LWASQ, Lehrer & Woolfolk, 1982) as measures of Anxiety; the Penn State Worry Questionnaire (Meyer et al, 1990) as a measure of Worry; the Bodily Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire (Chambless et al, 1984) as measures of Panic; the agoraphobia scale of the Fear Questionnaire (Marks

& Mathews, 1979) as a measure of Avoidance; the Beck Depression Inventory (Beck et al, 1961); the General Health Questionnaire-12 (Goldberg& Williams, 1988); and the Sheehan Disability Scale (Sheehan, 1983) as a measure of Social adjustment.

### **Statistical analysis**

The three treatments were compared at pretest for differences in demographic and psychiatric status variables. Outcome analyses were performed on an intent-to-treat basis. If an outcome value was missing, the pretest value was used to replace the posttest, follow-up 1 or follow-up 2 value. The analyses were repeated after excluding the dropouts.

Primary and secondary outcome measures were subjected to analysis of variance (ANOVA) using the General Linear Model with 3 x 2 repeated measures, with the 3 groups as between-subjects factor and the 2 evaluations (pretest and posttest) as within-subjects factor. The between-subjects factor was further broken down into two Helmert contrasts. The first contrast compared the mean change from pretest to posttest scores for CBT and Manual with that for Guidelines. The second contrast compared the mean change from pretest to posttest scores for CBT with that for Manual. These analyses were repeated on the mean change from pretest to follow-up 1 and from pretest to follow-up 2. Significant time effects for the primary and the secondary outcome measures were further analysed by means of paired t-tests (pretest versus posttest; pretest versus follow-up 1 and pretest versus follow-up 2) for each group separately. All statistical tests were two-tailed at alpha = 0.05, unless multiple test were performed in which case alpha was divided by the number of tests (Bonferroni correction) Data analysis were conducted using SPSS 11.0 (SPSS Inc, Chicago, IL).

## **Results**

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### **Recruitment and attrition**

Figure 1 shows the variation of the total trial population during the study and the reasons for dropping out. Completers and dropouts were evenly distributed over the three treatment groups ( $p>0.67$ ).

### **Characteristics of the participants**

Pretest demographic characteristics and psychiatric status variables of the study sample are presented in Tables 1 and 2. No statistical differences were found

between the various treatment groups, and no significant differences were found between dropouts and completers at pretest.

**Table 1: Pretest demographic characteristics of the study group**

	Treatment type		
	Manual	Cognitive behaviour therapy	Guidelines
Patients			
Total	53	63	26
Dropout (%)	6 (11)	9 (14)	2 (8)
Completer	47	54	24
Sex, male (%)	20 (38)	25 (40)	8 (31)
Mean age (SD)	38.8 (12.7)	38.0 (12.5)	38.8 (13.3)
Married	25 (47)	24 (38)	11 (42)
Employed	30 (57)	38 (60)	18 (69)
Higher education (%)	13 (25)	29 (46)	10 (38)
Main diagnosis			
Panic disorder (%)	12 (23)	12 (19)	8 (31)
Panic disorder and agoraphobia (%)	24 (45)	31 (49)	11 (42)
Generalised anxiety disorder (%)	17 (32)	20 (32)	7 (27)
Double diagnosis (PD and GAD) (%)	16 (30)	16 (25)	8 (31)
Mean duration in years of anxiety disorder (SD)	10.02 (13.21)	8.65 (11.54)	6.38 (9.17)

GAD = generalised anxiety disorder. Guidelines = anxiety disorder guidelines by the Dutch College of General Practitioners. Manual = guided self-help treatment. PD = panic disorder. SD = standard deviation. Note: No significant differences emerged between the three conditions.

## Outcomes

In the intent-to-treat sample, application of Helmert contrasts to the STAI state scores did not reveal significant differences between the two test points (pretest versus posttest; pretest versus follow-up 1; and pretest versus follow-up 2) or between the CBT and Manual treatments on the one hand and Guidelines on the other (between pretest and follow-up 2: effect size 0.06; 95% CI -5.3 - 2.5). No significant differences were found between CBT and Manual either (between pretest and follow-up 2: effect size 0.03; 95% CI -4.2 - 6.3). The same held for the analyses of the completer sample. Helmert contrasts yielded the same pattern of results for the secondary outcome measures (data not shown, the complete data can be obtained from the corresponding author). The three groups all improved significantly from pretest to posttest, pretest to follow-up 1 and pretest to follow-up 2 on all outcome measures. No significant differences were found between posttest and follow-up 1 or follow-up 2.

## **GPs' views on the feasibility of self-help (Manual) and Guidelines treatment**

GPs randomly assigned to the Manual treatment group were much more active in putting participants forward for the study than those assigned to Guidelines. Although 23 GPs participated in both treatment groups, 17 in the Guidelines group put forward a total of 88 possible participants while 19 GPs assigned to the Manual group put forward a total of 199 participants. All GPs were interviewed to identify the disincentive factors that were operative here. Most GPs stated that they felt unable to carry out even the simplified CBT laid down in the Guidelines, and that the time investment needed was too high. As a result, half of the participants were treated with antidepressants, and one third were referred to secondary care. The mean number of visits to the GPs in the 12-week treatment period was 5.4 (SD 3.3).

## **Discussion**

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### **Summary of main findings**

It may be concluded that panic disorder and generalized anxiety disorder can be effectively treated in primary care by a GP using the Guidelines or Manual method and by experienced cognitive-behaviour therapists in secondary care. We could not confirm our hypothesis that the effectiveness of the treatments was directly related to the complexity and intensity of the form of CBT given. The three treatments did not differ significantly in reducing anxiety and associated symptoms. The major part of the improvement was realised in the first 12 weeks of the study. The GPs in the Guidelines group referred less than half as many participants to the study than the GPs in the Manual group, since they knew there was a chance that their patients would be assigned to the Guidelines treatment which they would have to deliver. The feasibility of Guidelines was rather low, because the GPs concerned felt incapable of delivering it or found it too time-consuming. It appeared that about half of the patients did not actually receive the intended CBT. Instead, they were treated with antidepressants and/or referred to secondary care. The gold standard, CBT in secondary care carried out by experienced therapists, was however not superior to the treatments carried out by GPs. Apparently primary care patients with anxiety disorders, whose GP does not consider referral to secondary care necessary, can receive optimal care from their GP. A more intensive secondary care treatment does not improve the outcome.

## Strengths and limitations of the study

The results of this study suggest that Manual may be a feasible and effective treatment for panic disorder and generalized anxiety disorder in primary care. The effectiveness of Manual was comparable to that of the gold standard, CBT performed by professionals in secondary care. The improvement brought about by Manual treatment was maintained during 40 weeks of follow-up. Our results can be generalized to primary care patients with panic disorder and generalized anxiety disorder. Case finding in this study was performed by the GP during normal practice, instead of screening general practice patients in the waiting room. Moreover, the anxiety disorders in this study were diagnosed in a valid way by means of a structural interview.

A limitation of our study was the low feasibility found for Guidelines. As a consequence the sample size in this group only reached half the size originally intended. Therefore, it is difficult to draw definite conclusions about this intervention. We do not think, however, that the inclusion of only 26 participants from this group in the study population has led to a type II error (failure to reject a false null hypothesis). Inspection of the data and the confidence intervals did not reveal any differences between the three treatment groups which might have become significant if the sample size had been larger. To avoid further divergence of the size of the cells, we decided halfway through the study to change the randomisation ratio in practices randomly assigned to the Manual treatment group. We cannot rule out the possibility that this change in the randomisation ratio has biased our results. However, such bias seems unlikely since no differences were found in post-hoc statistical analyses before and after this intervention.

## Comparison with existing literature

The finding that CBT in secondary care was not superior to Manual was rather unexpected. Our study is the first in which these two treatments were compared in a single trial. The lack of difference found between CBT and Manual might be due to the fact that participants in both groups were given an equal number of hours of homework, or to the fact that the patients treated are taken from primary care, i.e. will on average only have relatively mild complaints for which formal CBT may represent 'over-treatment'. Another unexpected finding was the effectiveness of Guidelines. However, more than half of the patients assigned to this treatment group did not in fact receive this simple form of CBT but were given antidepressants or referred to secondary care. While Guidelines may be suitable for motivated GPs, it seems that in the Netherlands most GPs do not have the affinity

with or knowledge of this approach - or the time - to give even simple CBT exercises to their anxiety disorder patients.

### **Implications for clinical practice**

Our results indicate that primary care patients with panic disorder and generalized anxiety disorder may be treated effectively by the GP and that referral to psychiatric outpatient clinic does not yield better results. Moreover, Manual is easier to carry out by a GP than a less structured treatment such as Guidelines, and results in fewer referrals to specialised care.

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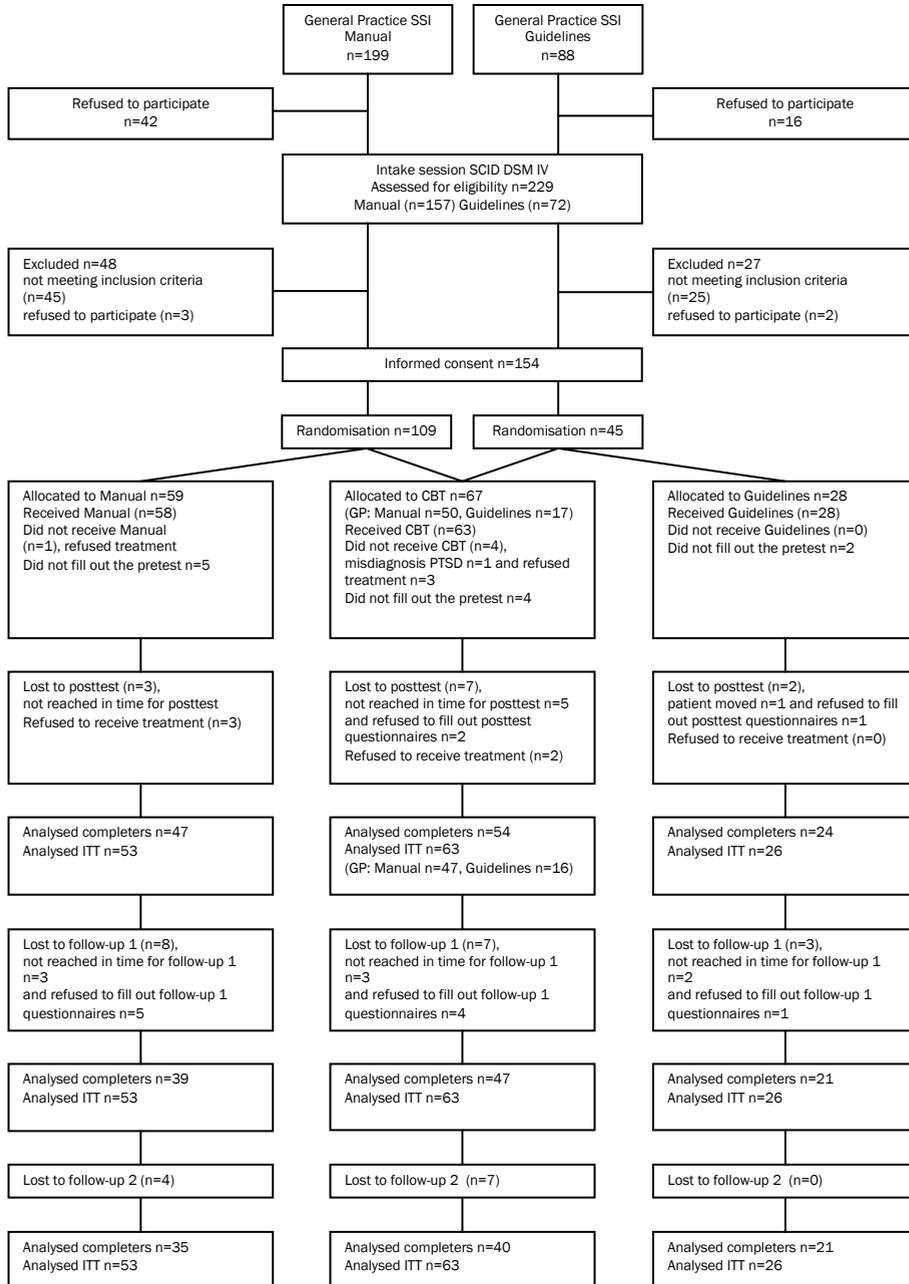
### **Ethics committee**

The Medical Ethics committee of the VU University Medical Centre ref. number (95/174)

### **Competing interests**

None

Figure 1: Recruitment to analysis



CBT = cognitive behaviour therapy. ITT = Intention-to-treat

Table 2: Pretest, posttest, follow-up 1 and follow-up 2 clinical characteristics of study group (intention-to-treat sample)

Scales	range	Treatment type					
		Manual (n=53)		Cognitive behaviour therapy (n=63)		Guidelines (n=26)	
		Mean	SD	Mean	SD	Mean	SD
<b>Anxiety</b>							
STAI State	20-80						
pretest		52.0	13.7	47.7	12.7	52.6	12.0
posttest		47.0	13.6	41.3	12.4	40.5	9.8
follow-up 1		44.3	12.5	40.6	13.0	42.9	10.5
follow-up 2		42.9	12.8	40.6	14.2	38.8	11.5
STAI Trait	20-80						
pretest		55.5	8.8	51.2	11.7	55.8	8.2
posttest		48.9	11.9	45.3	12.1	46.8	9.6
follow-up 1		46.6	12.0	43.0	13.2	45.3	11.9
follow-up 2		44.6	11.8	42.7	13.2	41.3	10.6
LWASQ Somatic	16-80						
pretest		45.5	11.6	39.3	13.0	41.8	11.6
posttest		36.6	12.3	32.6	13.4	33.8	11.7
follow-up 1		34.6	12.1	31.1	13.4	31.2	12.2
follow-up 2		33.7	11.7	31.9	15.0	29.7	12.2
LWASQ Behaviour	9-45						
pretest		20.4	8.2	19.6	7.9	19.7	7.1
posttest		18.0	7.5	17.8	7.6	17.4	5.6
follow-up 1		16.8	6.6	17.2	7.4	16.3	5.0
follow-up 2		16.5	7.6	17.6	8.6	14.4	5.8
LWASQ Cognition	11-55						
pretest		33.7	9.2	30.2	9.0	31.2	8.7
posttest		28.4	9.8	25.4	9.2	26.2	8.7
follow-up 1		27.2	9.4	24.2	9.8	23.1	8.5
follow-up 2		26.3	9.8	24.4	10.4	20.6	8.7
<b>Worry</b>							
PSWQ	16-80						
Pretest		59.7	12.8	54.7	12.9	60.0	10.5
Posttest		53.9	12.7	50.3	13.1	51.8	11.9
follow-up 1		53.2	12.2	48.7	13.4	50.1	14.4
follow-up 2		51.9	12.8	47.5	12.9	46.6	11.7
<b>Panic</b>							
BSQ 1	17-85						
pretest		42.8	15.3	38.5	13.4	43.5	11.0
posttest		36.1	13.0	32.4	11.9	36.4	13.1
follow-up 1		35.7	13.7	31.9	13.0	36.5	15.2
follow-up 2		34.1	13.1	32.6	14.9	33.5	14.0
BSQ2	17-85						
pretest		43.7	10.4	42.5	12.0	43.3	9.6
posttest		38.0	10.6	37.3	12.6	38.5	11.8
follow-up 1		36.3	11.4	34.7	11.8	35.9	11.3
follow-up 2		35.5	11.8	34.8	13.4	32.6	10.4
ACQ	14-70						
pretest		28.6	9.9	28.1	10.1	28.6	10.9
posttest		25.1	9.3	24.4	8.9	24.7	9.2
follow-up 1		23.9	8.6	23.2	9.3	23.7	9.8
follow-up 2		23.6	9.3	22.7	9.5	21.1	6.9

Table 2 continues on the next page...

Table 2 continued

Scales	range	Treatment type					
		Manual (n=53)		Cognitive behaviour therapy (n=63)		Guidelines (n=26)	
		Mean	SD	Mean	SD	Mean	SD
<b>Avoidance</b>							
FQ Agoraphobia	0-40						
pretest		12.8*	11.6	10.6	10.4	14.0	11.4
posttest		11.2*	10.8	6.7	8.1	10.3	10.0
follow-up 1		9.4	10.5	6.6	9.5	8.5	8.5
follow-up 2		9.1	10.8	5.9	9.0	6.5	7.2
<b>Depression</b>							
BDI	0-63						
Pretest		16.4	9.7	14.8	8.4	12.6	6.1
Posttest		12.0	9.1	9.8	8.2	8.4	6.9
follow-up 1		11.1	8.4	9.6	8.7	8.6	8.5
follow-up 2		10.3	7.9	9.3	8.3	7.2	4.9
<b>General health</b>							
GHQ-12	0-12						
Pretest		7.1	3.7	5.4	4.1	7.4	3.5
Posttest		3.8	4.3	2.4	3.2	3.0	4.0
follow-up 1		3.4	4.0	2.3	3.4	2.8	3.7
follow-up 2		3.2	3.9	2.4	3.4	2.1	3.2
<b>Disability</b>							
SDS Work	0-10						
Pretest		6.1	3.0	5.5	3.0	5.7 <sup>a</sup>	3.0
Posttest		4.9	3.2	3.5	3.3	4.6 <sup>b</sup>	2.6
follow-up 1		4.1	3.3	3.1	3.3	3.8	3.0
follow-up 2		3.6	3.2	3.2	3.4	2.9	2.8
SDS Social/Leisure	0-10						
Pretest		6.6	2.4	5.2	2.7	6.5	2.3
Posttest		4.8	3.3	3.3	2.9	4.8	3.0
follow-up 1		4.3	3.0	3.1	2.9	4.4	2.9
follow-up 2		3.8	2.8	3.0	3.0	3.4	2.7
SDS Family/Home	0-10						
Pretest		6.0	2.4	4.6	3.0	5.3	2.8
Posttest		3.6	3.0	2.9	2.9	3.0	2.5
follow-up 1		3.7	3.0	2.6	3.0	3.5	3.0
follow-up 2		3.3	3.2	2.6	3.1	2.9	2.6

ACQ = Agoraphobic Cognitions Questionnaire. BDI = Beck Depression Inventory. BSQ = Body Sensation Questionnaire. FQ = Fear Questionnaire. GHQ = General Health Questionnaire. Guidelines = Anxiety Disorder Guidelines of the Dutch College of General Practitioners. LWASQ = Lehrer Woolfolk Anxiety Symptom Questionnaire. Manual = Guided Self-Help Treatment. PSWQ = Penn State Worry Questionnaire. SD = standard deviation. SDS = Sheehan Disability Scale. STAI = Spielberger State-Trait Anxiety Inventory. No significant differences emerged between the pretest scores of the three conditions. <sup>a</sup>No significant time effect (pre-posttest) in Manual condition for avoidance (FQ)  $p=.131$ . <sup>b</sup>No significant time effect (pre-posttest) in Guidelines condition for SDS work  $p=.066$ . Note: for all other measurements significant time effect (pre-posttest; pre-follow-up 1; and pre-follow-up 2) on all conditions.

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## Chapter 5

# Comorbid depression predicts outcome

Comorbid depression but not comorbid anxiety disorders predict poor outcome in anxiety disorders

This chapter been submitted for publication :

van Balkom AJLM, van Boeijen CA, Boeke AJP, van Oppen P, Kempe PT, van Dyck R. Comorbidity depression but not comorbid anxiety disorders predicts poor outcome in anxiety disorders

### Abstract

#### Objective

To study the influence of type of comorbidity on the 1-year course of a sample of 141 outpatients with panic disorder with or without agoraphobia and generalized anxiety disorder receiving different forms of cognitive behaviour therapy.

#### Methods

Influence of type of comorbidity was determined on change scores (linear regression analysis) and remission data (Kaplan-Meier survival analysis). Three categories as assessed at pretest were compared: no comorbidity, comorbidity among anxiety disorders and comorbidity with mood disorders. Primary outcome variable: State-Trait Anxiety Inventory State subscale measured at four assessments (0, 12, 24 and 52 weeks).

**Results**

Analyses on change and on remission indicated that comorbidity with mood disorders led to (i) less improvement and (ii) a smaller remission rate than comorbidity among anxiety disorders and no comorbidity. No significant difference emerged between the 'no comorbidity' group and the 'comorbidity among anxiety disorders' group.

**Conclusions**

Because comorbidity critically influences prognosis, it appears to be important to reliably diagnose the disorders present. In patients with anxiety disorder and comorbid mood disorders cognitive behavioural therapy may be not the first choice treatment.

**Keywords**

Anxiety disorders, depression, comorbidity, cognitive behavioural therapy, long-term outcome, follow-up

## Introduction

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Recent studies into the patterns of comorbidity of anxiety disorders have revealed that comorbidity (i) among the anxiety disorders (Brown & Barlow, 1992; Bijl et al, 1997; van Balkom et al, 2000) and (ii) between anxiety and mood disorders (Brown & Barlow, 1992; Bijl et al, 1997; van Balkom et al, 2000; Pirkola et al, 2005) is the rule rather than the exception. This finding has led to criticism of the present diagnostic system from European and Australian clinicians (Andrews, 1996; Tyrer et al, 2004; Maj, 2005), stating that so-called 'comorbidity' is a consequence of the splitting of the neurosis concept into several anxiety and mood disorders with the introduction of DSM-III in 1980 and the subsequent proliferation of the number of diagnostic categories in the next versions of the DSM system. Moreover, 'comorbidity' would be an artificial by-product of overlapping symptom patterns revealed with the use of standardised diagnostic interviews (Maj, 2005). However that may be, it has been found repeatedly that patients with comorbid anxiety and mood disorders have more severe complaints (Andrade et al, 1994; Grunhaus et al, 1994; Kessler et al, 1994; Brown et al, 1995; van Balkom et al, 2000), a higher utilisation of services (Kessler et al, 1994; Jacobi et al, 2004) and poorer outcome of treatment focussed on the anxiety disorder (Keijsers et al, 1994; Pollack et al, 1994; Corominas et al, 2002; Shankman, 2002).

Surprisingly, the influence of comorbidity among the anxiety disorders on the course of the (index) anxiety disorder has received little attention. As far as we know, only one study has focussed on the differential influence of comorbidity among anxiety disorders vs. comorbidity between anxiety and mood disorders (Bruce et al, 2005). In this study with a clinical sample it was found that comorbidity of generalised anxiety disorder or depressive disorder negatively influenced recovery rates in patients with panic disorder with agoraphobia but not in panic disorder. Moreover, the effect of comorbid generalised anxiety disorder affected the course of social phobia negatively, in contrast to comorbid depressive disorder (Bruce et al, 2005). Unfortunately, this study did not take into account the number of diagnoses present. Thus, the debatable question remains whether it is the presence of comorbidity in itself (cf. the number of diagnoses), or rather specific comorbidity that negatively influences anxiety disorder treatment outcome. We were able to study this problem in a sample of patients with panic disorder and/or generalised anxiety disorder and psychiatric comorbidity treated with cognitive behavioural therapy in general practice or specialised secondary care.

## Methods

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### Design

In a 12-week randomised controlled trial the effectiveness of three treatment modalities in panic disorder with or without agoraphobia (PA) or generalised anxiety disorder (GAD) was compared: (i) referral to secondary care for cognitive behavioural therapy (CBT) provided by experienced therapists versus treatment in primary care practice by the general practitioner (GP) with (ii) a guided self-help CBT manual for PA or GAD or (iii) treatment according to the anxiety disorder guidelines of the Dutch College of General Practitioners. Follow-up I was scheduled at 24 weeks after a treatment-free period while a naturalistic follow-up II was scheduled at 52 weeks. The study was approved by the Medical Ethics committee of the VU University Medical Centre, Amsterdam, The Netherlands, and was performed from February 1998 to May 2002. The results of the randomised controlled trial are reported elsewhere in detail and are therefore summarized only briefly here (Van Boeijen et al, 2005).

### Outcome

Included were 141 participants over 18 years of age, recruited from general practices in rural and urban areas of the Netherlands, who met DSM-IV criteria for PA or GAD. To confirm the diagnosis and to determine the presence of comorbid diagnoses, participants were interviewed with the Structured Clinical Interview for DSM-IV (SCID-IV; First et al, 1997). Exclusion criteria were presence of an organic mental disorder; mental retardation or psychotic disorder; use of antidepressants or the use of more than 30mg oxazepam equivalents daily.

All participants received individual 12-week treatment based on cognitive-behavioural principles. The three treatment categories differed mainly in intensity and complexity. All treatments included psycho-education about anxiety and the rationale of CBT, identification of anxiety-provoking cognitions, challenging these cognitions and replacing them by more realistic and rational cognitions, behavioural experiments, relaxation techniques and in vivo exposure exercises (Emmelkamp et al, 1989). Specialised care with CBT was the most intensive treatment, comprising twelve 45-minute sessions and three hours homework per week. Treatment by the GP with the guided self-help manual consisted of five 20-minute sessions (Van Boeijen et al, 2005; Van Boeijen et al, in press). Treatment according to the anxiety disorder guidelines was the least structured form of treatment, and consisted of a very simple form of CBT. The GP was free to choose

the number of sessions and the type of intervention, but was advised to start with explanation about the nature of anxiety followed by reassurance, simple cognitive techniques and in vivo exposure. (Neomagus, 1997: updated Terluin et al, 2004)

Participants filled out questionnaires at pretest, 12 weeks (posttest), 24 weeks (follow-up I) and 52 weeks (follow-up II). The state subscale of the Spielberger State Trait Anxiety Inventory (STAI-State; Spielberger et al, 1970) was the primary outcome measure. Outcome in the completer sample and intent to treat sample was identical: the three treatment categories gave significant and clinically relevant improvement between pretest and posttest. This improvement remained stable between posttest and follow-up I respectively follow-up II. The effectiveness of the three treatments did not differ significantly on any moment. Thus, for the present study, the results of the three treatment categories were lumped together.

## Participants

Of the 141 participants included, two were excluded from the statistical analyses because of outlying pretest scores of more than 2 standard deviations from the mean on the STAI-State. Moreover, given the definition for remission used in this study, both patients almost could be considered 'remitted' at pretest. Both participants belonged to the group anxiety disorders with comorbid mood disorders (see further). One of these participants was diagnosed with 6 comorbid diagnoses and had a pretest score of 36 on the STAI-State. The second participant was diagnosed with 7 comorbid diagnoses and scored 35 on the STAI-State at pretest.

To study the influence of comorbidity, participants were divided into three groups according to the diagnoses determined with the SCID at pretest: (i) no-comorbidity (n=65) including only participants diagnosed with PA (n=50) or GAD (n=15), (ii) comorbidity among anxiety disorders (n= 56), including all participants diagnosed with PA or GAD, at least one comorbid anxiety disorder and no comorbid mood disorder, and (iii) comorbidity with mood disorders (n=18), including those patients with at least one anxiety disorder and a comorbid depressive disorder (n=16), dysthymia (n=1), and depressive disorder with comorbid dysthymia (n=1).

## Remission

Based on population scores, remission was defined as a score on the STAI-State lower than 34 (Van der Ploeg, 1980). This score is derived from validation studies of the STAI-State in the Netherlands with a population of healthy medical students. In rest, 96 healthy male students had a mean score of 34.3 (SD = 7.3)

versus a mean score of 33.7 (SD = 6.7) in 59 females. Comparing these scores with STAI-state score under stress in healthy medical students of mean 43.3 (SD = 10.3) in males versus mean 45.1 (SD = 11.8) in females and anxiety disorder outpatients of 45.0 (SD = 10.2) in males and 51.8 (SD = 10.8) in females, it can be concluded that the definition of remission used was rather conservative.

## Statistical analysis

The three groups were compared at pretest for differences in demographic and psychiatric status variables with one-way ANOVA or Chi square tests. Treatment effect on the STAI-State was analysed within each group with paired t-tests, comparing pretest with posttest, follow-up I or follow-up II.

The influence of comorbidity on treatment outcome was analysed with (i) change scores and (ii) remission data. To delineate change in anxiety scores on the STAI-State over time the 'residual gain score' was used as this score is more reliable compared with a 'raw' change score. Moreover, the residual change score corrects for the influence of the pretest level on the raw change score. The influence of comorbidity on the residual gain score was evaluated using linear regression analysis with the residual gain score on the STAI-State as the dependent variable and group as independent variable. These analyses were done comparing pretest with posttest, pretest with follow-up I and pretest with follow-up II.

To analyse whether the course of remission across the three groups differed critically, Kaplan-Meier survival analyses were performed with patients with a score on the STAI-State of 34 and lower considered as remitted.

Due to the relatively small sample size, only univariate analyses were run. All analyses were done on an intent-to-treat basis (n=139). For this analysis missing outcome values were substituted by the last value obtained. These analyses were repeated in the completer sample (n=109), but because the results of the intent to treat analyses corroborated the completer analyses, only the former are discussed.

## Results

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### Characteristics at pretest

Characteristics at pretest are presented in Table 1. The intent to treat sample (n=139) consisted of 52 males and 87 females with a mean age of 39 years (SD = 13 years). The three groups differed significantly on the proportion of patients

employed, the proportion of patients with comorbid GAD, the proportion of patients with comorbid obsessive compulsive disorder (OCD), and the mean number of SCID diagnoses. By definition, in the 'no comorbidity' group the number of SCID diagnoses was 1 and significantly smaller than the mean number of SCID diagnoses in the other two groups. In addition, the mean number of SCID diagnoses in the group 'comorbidity among anxiety disorders' was significantly smaller than the mean number of SCID diagnoses in the group 'comorbidity with mood disorders'.

**Table 1: Pretest demographic characteristics of the comorbidity groups (intent-to-treat sample)**

	No comorbidity (i) n=65	Comorbidity among anxiety disorders (ii) n=56	Comorbidity with mood disorders (iii) n=18
Sex, male (%)	29(45)	18(32)	5(28)
Mean age (SD)	37.5(12.0)	38.6(13.5)	41.8(12.8)
Married (%)	26(40)	25(45)	7(39)
Employed (%)	42(65) <sup>a</sup>	27(48)	6(33) <sup>a</sup>
Higher education (%)	24(37)	22(39)	5(28)
Diagnosis (%)			
Panic Disorder with/without Agoraphobia	50(77)	47(84)	16(89)
Generalized Anxiety Disorder Agoraphobia	15(23) <sup>a</sup>	42(75) <sup>ac</sup>	7(39) <sup>c</sup>
Social Phobia	33(51)	28(50)	13(72)
Obsessive Compulsive Disorder	0 <sup>ab</sup>	9(16) <sup>a</sup>	4(22) <sup>b</sup>
Simple Phobia	0 <sup>b</sup>	3(5) <sup>c</sup>	5(28) <sup>c</sup>
Post Traumatic Stress Disorder	0 <sup>a</sup>	7(13) <sup>a</sup>	2(11)
Depression	0 <sup>b</sup>	2(4)	3(17) <sup>b</sup>
Dysthymia	0 <sup>b</sup>	0 <sup>c</sup>	17(94) <sup>bc</sup>
Hypochondriasis	0	0	2(11%)
Boulimia Nervosa	0 <sup>ab</sup>	6(11) <sup>a</sup>	2(11) <sup>b</sup>
Substance Dependence	0	1(2)	0
Adjustment Disorder	0 <sup>ab</sup>	7(13) <sup>a</sup>	3(17) <sup>b</sup>
Adjustment Disorder	0	2(4)	0
Mean number of diagnosis (SD)	1(0) <sup>ba</sup>	2.3(.7) <sup>ac</sup>	3.4(1.3) <sup>bc</sup>
Mean duration in years of anxiety disorder (SD)	7.5(10.3)	9.7(12.9)	9.4(13.7)
Randomisation to secondary care (%)	33(51)	23(41)	5(28)

SD=Standard Deviation. <sup>a</sup>= significant difference between no comorbidity group and comorbidity among anxiety group. <sup>b</sup>= significant difference between no comorbidity group and comorbidity with mood disorder group. <sup>c</sup>= significant difference between comorbidity among anxiety group and comorbidity with mood disorder group.

In Table 2 mean scores on the STAI-State are shown for the three groups on the four measurements. The three groups improved significantly between pretest and posttest. Between posttest and the two follow-ups in none of the three groups

significant improvements emerged. Of the three groups, the group 'comorbidity with mood disorders' had the most severe score on all measurements, while the 'no comorbidity' group had the least severe scores. The group 'comorbidity among the anxiety disorders' occupied an intermediate position on the four measurements.

Table 2: Pretest, posttest, follow-up 1 and follow-up 2 STAI-State of study group (intent to treat-sample) and One way ANOVA

Scale	range	No comorbidity (i) n=65		Comorbidity among anxiety disorders (ii) n=56		Comorbidity with mood disorder (iii) n=18		One way ANOVA
		Mean	SD	Mean	SD	Mean	SD	
STAI State	20-80							
pretest		46.2	13.4	52.2	12.2	60.2	7.4	1<2;1<3
posttest		40.9	13.1	43.6	11.2	52.3	12.3	1<3;2<3
follow-up 1		39.0	12.2	43.8	11.6	51.5	10.4	1<3
follow-up 2		38.0	12.4	42.6	12.6	50.7	12.7	1<3

n=number of patients. ANOVA=Analysis Of VAriance SD=Standard Deviation. STAI=Spielberger State-Trait Anxiety Inventory. Significant time effect (pretest-posttest/pretest- follow-up 1/pretest- follow-up 2) in the no comorbidity group, the comorbidity among anxiety disorders group and the comorbidity with mood disorders group. The greatest time-effect is find between pretest and posttest and stayed in most of the groups stable during follow-up period.

## Attrition

Participants were considered dropout when they did not fill out follow-up II. From pretest to follow-up II test 8 of 65 participants (12%) were considered dropouts in the 'no comorbidity' group versus 18 of 56 participants (32%) in the group 'comorbidity among the anxiety disorders' and 4 of 18 participants (23%) in the group 'comorbidity with mood disorders' (Chi square (df = 2) = 7.0; p = .03). Dropouts (n=30) did not differ significantly from the completers (n=109) on any variable presented in the Tables 1 and 2. For an overview see Figure 1.

## Influence of comorbidity on change scores

To analyse whether the improvement among the three groups differed, three regression analyses were done on the STAI-State with the residual gain scores between pretest and posttest, pretest and follow-up I and pretest and follow-up II as the dependent variable and group as independent variable. Relative improvement diverged critically across the three groups between pretest and follow-up I respectively pretest and follow up II (pretest vs. posttest: F (df = 2) = 34.41; p = .35; pretest vs. follow-up I: F (df = 2) = 27.71; p = .03; pretest vs. follow-

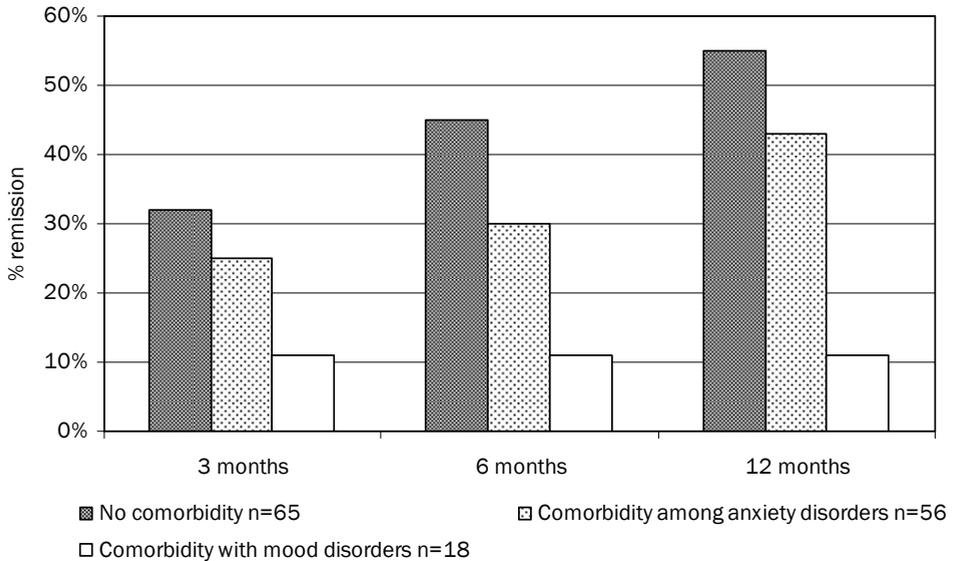
up II:  $F(df = 2) = 21.58$ ;  $p = .04$ ). Pairwise comparisons indicated that the group 'comorbidity with mood disorders' improved less between pretest and follow-up I respectively pretest and follow-up II compared with the improvement of the 'no comorbidity' group and the 'comorbidity among anxiety disorders' group (due to the small sample size of the 'comorbidity with mood disorders' group, these pairwise comparisons yielded trends only:  $0.05 < p < 0.13$ ).

### **Influence of comorbidity on remission**

In figure 2 the percentages of remission across the three groups on the STAI state are shown. Kaplan-Meier survival analysis revealed significant differences across the three comorbidity groups (Log Rank: 10.16 ( $df=2$ );  $p=.006$ ). Pairwise comparisons showed significant differences: 'no comorbidity' vs. 'comorbidity with mood disorders' (Log Rank: 9.53 ( $df=1$ );  $p=.002$ ; Relative Risk (R.R.): 5.0; 95% Confidence Interval (95% C.I.): 2.11-46.74); 'comorbidity among anxiety disorders' vs 'comorbidity with mood disorders' (Log Rank: 5.38 ( $df=1$ );  $p=.020$ ; R.R.: 3.91; 95% C.I.: 1.25-28.5). No significant difference emerged between the 'no comorbidity' group and the 'comorbidity among anxiety disorders' group (Log Rank: 2.04 ( $df=1$ );  $p=.15$ ; R.R.: 1.3; 95% C.I.: 0.80-3.40). To study whether correcting for pretest scores on the STAI-State influenced the results on the remission rates, Cox regression analyses were performed with the STAI-State pretest score entered into the regression analysis in the first step, followed by 'group'. Now, the three groups did not differ significantly any more on remission rates.

In addition, Kaplan-Meier survival analyses were run for each of the possible confounding variables (i.e. those variables with significantly different scores between 'comorbidity among anxiety disorders' and 'comorbidity with mood disorders'; see Table 1). None of these variables yielded different remission rates among the three groups: employment (Log Rank 1.10 ( $df=1$ );  $p=.29$ ), proportion of GAD (Log Rank 1.58 ( $df=1$ );  $p=.21$ ), proportion of OCD (Log Rank 0.57( $df=1$ );  $p=.45$ ), and the number of SCID diagnoses divided into 6 groups did not appear to be associated with remission (Log Rank 9.14 ( $df=5$ );  $p=.10$ ).

Figure 2: Remission to normal value on STAI state in three specific comorbidity categories



## Discussion

It may be concluded that in a sample of primary care PA and GAD patients type of comorbidity critically influenced outcome of cognitive behavioural therapy: (i) Although all groups improved, the patients in the groups 'no comorbidity' or 'comorbidity among the anxiety disorders' improved more than those with 'comorbidity with mood disorders'. (ii) Moreover, the groups 'no comorbidity' or 'comorbidity among the anxiety disorders' had at least a four times higher chance to remit than those with 'comorbidity with mood disorders' (apart from the index anxiety disorder). In contrast, the residual gain scores and the remission scores of the groups 'no comorbidity' and 'comorbidity among the anxiety disorders' did not differ critically. In addition, in the present study it was found that patients with anxiety disorders with comorbid mood disorders suffer from more severe anxiety symptoms. During the whole follow-up period, this group remained the most severe.

Our results fit well in the existing literature on the influence of comorbidity between anxiety and mood disorders: it has been found repeatedly that patients

with comorbid anxiety and mood disorders have more severe complaints (Andrade et al, 1994; Grunhaus et al, 1994; Kessler et al, 1994; Brown et al, 1995; van Balkom et al, 2000) and poorer outcome of treatment focussed on the anxiety disorder (Keijsers et al, 1994; Pollack et al, 1994; Corominas et al, 2002; Shankman, 2002). Our results expand on the literature by the finding that not comorbidity in itself necessarily affects severity and outcome negatively, but rather type of comorbidity. The results of the present study suggest that comorbidity of anxiety and mood disorders has a more negative influence than comorbidity among the anxiety disorders.

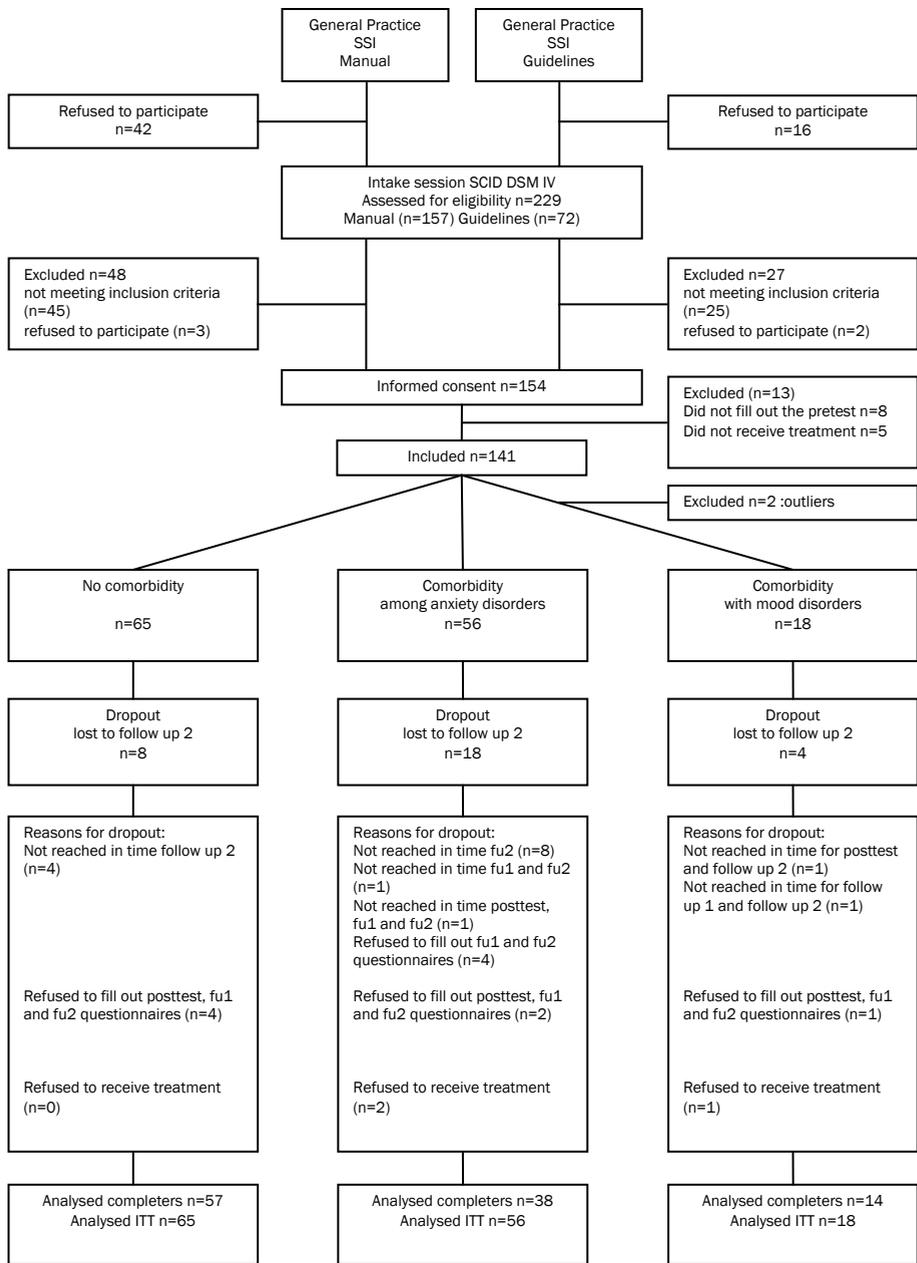
The influence of type of comorbidity on outcome could be studied in this RCT and its 52-week follow-up, because pure and comorbid patients with panic disorder with or without agoraphobia or generalised anxiety disorder were included. We chose to increase the external validity of our results by including comorbid patients because clinicians often point at the problem of translating the results of RCT's to their daily practice. They justly point out that they are confronted only rarely with the kind of 'pure' patients usually selected for standard RCT's. Recently, this criticism has been confirmed by a study which found that only 14% of patients with a depressive disorder with a strict clinical profile qualified for a RCT with antidepressants (Zimmerman et al, 2002). Due to the broad inclusion criteria of the present study we could include patients comparable with those of every day practice.

A limitation of this study is the relative small sample size (especially in the group 'comorbidity with mood disorders') resulting in reduced statistical power. Thus, we could not control in statistical analyses for confounding variables, such as the rate of employment, the proportion of patients with comorbid GAD, the proportion of patients with comorbid OCD and the mean number of diagnoses which differed significantly across the three groups. However, in univariate Kaplan-Meier analyses we could not find significant relations between these variables and remission rates. Another limitation holds the type of treatment studied here: all patients received a form of cognitive behavioural therapy. It may be that in case the patients comorbid with mood disorders would have been treated with antidepressants, outcome would have been better. Given these limitations, the present results await corroboration from future research.

Despite the small sample size, the results suggest indicate a differential effect of type of comorbidity. The presence of mood disorders with anxiety disorders predicts poorer treatment outcome compared with the presence of one or more anxiety disorders. The data suggest that rather than the number of comorbid

disorders, type of comorbidity critically predicts outcome. These findings have major implications for clinical practice: First, it appears to be important to reliably diagnose comorbid mood disorders when anxiety disorders are present because this critically influences prognosis. Second, in anxiety disorder patients with comorbid mood disorders cognitive behavioural therapy alone may not be the most adequate treatment.

Figure 1: Recruitment to analysis



CBT = cognitive behaviour therapy. ITT = Intention-to-treat

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# **CONCLUSION**

GENERAL DISCUSSION • CHAPTER 6



## Chapter 6

# General discussion

### Introduction

In this final chapter the main findings and conclusions of this study are critically discussed. The main purpose of this study was to investigate the potential of self-help treatment for anxiety disorders in primary care. Anxiety disorders are prevalent in primary care and the number of studies targeted at this population is limited, while it is evident that treatments designed for secondary care are usually not feasible for primary care because they require too much time investment. In the Guidelines for treatment of anxiety disorders developed by the Dutch College of General Practitioners (referred to henceforth as Guidelines), self-help is not mentioned as an option, which motivated us to this study. From a literature review it followed that self-help shows sufficient effectiveness, but that results improve when some additional time is available from a supporting figure such as a general practitioner (GP) to keep the patients on the self-help program. Subsequently, we developed a self-help manual for two prevalent anxiety disorders in primary care, panic disorder with or without agoraphobia and generalized anxiety disorder, which included guidance from the GP, resulting in guided self-help treatment (referred to from now on as Manual). In a number of n=1 studies we found that Manual was feasible and led to improvement in the primary care patients treated.

The main goal of the study was to compare the effectiveness of a guided self-help treatment for panic disorder and generalized anxiety disorder with the Guidelines of the Dutch College of General Practitioners. As these Guidelines have not yet been studied for their effectiveness, Cognitive Behaviour Therapy as practiced in secondary care was used as a third condition and as “gold standard”. A special feature of this study was that primary care treatments for primary care patients were compared to a secondary care treatment for the same population. It was expected that Cognitive Behaviour Therapy delivered by experienced therapists, as evidence based secondary care therapy, would be more effective than Manual or Guidelines as delivered by the GP's. The main finding of the RCT comparing CBT,

Manual and Guidelines was that no difference in outcome was observed between the three treatment types.

We also investigated the effect of comorbidity on long term outcome and found that comorbidity with depression led to a lower rate of remission, while comorbidity with other anxiety disorders did not.

In this chapter, we will discuss the strengths and weaknesses of several aspects of the study. First the recruitment procedure of general practitioners and patients will be reviewed. The next topics will be the specific disorders chosen in the study and the differences in diagnostic procedures in primary and secondary care. The outcomes for the different treatment types will be discussed. In conclusions, we will consider the relevance of this study for clinical practice and make some suggestion for further research.

## **Recruitment of general practitioners and patients**

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GP's have had a central role in this study. They were asked to participate actively in the recruitment of patients, to follow training instructions and to conduct the treatment of their patients according to either the Manual or the Guidelines.

It proved to be rather difficult to find enough GP's who were willing to collaborate in this project. GP's were approached by written invitation and through personal contact. Participation of one member of a group practice often led to participation of other members of that group. Practitioners with little affinity for mental health problems tended not to enrol in the study. Randomisation at the practice level was chosen in order to avoid contamination between the treatment conditions (Hox, 1995). Although recruitment was limited to the Amsterdam region, some GP's refused participation because of the distance of their practice to the clinic where the training was given. For the above reasons, we cannot claim that the GP's participating in the study are entirely representative for GP's in general, which limits the generalisability of our study.

Another factor that limits generalisability is that GP's who were randomised to the Guidelines tended to lose interest in the study and enrolled fewer patients than their colleagues randomised to the Manual. Some GP's expressed their disappointment at not being allotted to the Manual, which clearly had more appeal because it was new. Other reasons given for not including more patients were that the right type of patients were not seen in the practice, patient refusal or the need

to start treatment without any delay. Since these reasons were invoked more often in the Guidelines than in the Manual, a difference in motivation suggests itself. Despite efforts as suggested in the literature (Murphy et al, 1992) to keep up the involvement of all GP's by newsletters, meetings and personal contact, the recruitment of patients remained unbalanced with a lower influx in the Guidelines group. This problem is not unusual when one wishes to compare a new treatment with care as usual, but a marked difference in referral patterns weakens the internal validity of a study. A partial solution to this imbalance would be to include more GP's in the condition that is expected to deliver less referrals. Although we did try to correct the imbalance by recruiting extra GP's, with an uneven ratio of randomisation over Manual and Guidelines, an equal distribution of patients over the three cells was not achieved. If one chooses to completely eliminate the influence of the person of the GP and his preferences, a recruitment procedure must be organised in which the GP plays no selecting role and treatment must be delivered by other therapists. This, of course, seriously endangers the external validity of any primary care treatment study. However, as no differences in outcome were found between the treatments, the consequences of this unbalance seem to be limited. A more serious problem of interpretation would have arisen if Manual would have had a better outcome than the Guidelines.

## **Screening and diagnosis**

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Selection of patients was initiated by the GP when there was a suspicion of an anxiety disorder. The GP then screened the patient with the Short and Simple Screening Interview (SSI) by Goldberg et al (1988). GPs were previously trained in the use of this instrument. Patients with a score of 5 or more were referred to the study for further diagnosis. This consisted of a two- hour interview including a SCID-IV diagnostic interview (First et al, 1997) to establish a DSM-IV diagnosis. The interview was conducted by diagnosticians in the out patient department of psychiatry. A number patients were lost to the study through this procedure. For some, the time involved was more than they wished to make available and for others it was too threatening to visit a psychiatric department. In retrospect, this could have been avoided by organising the diagnostic session in the GP's practice. This would, of course, have involved more travelling time for the diagnosticians. On the other hand, interview time might have been shortened by using a less time consuming instrument than the SCID-IV, such as the PRIME-MD (Spitzer et al, 1994) or the Anxiety Disorder Interview Schedule (ADIS; Brown et al, 2001). Organizing the diagnostic procedure within the primary care practice probably would have benefited the recruitment rate of this project.

## **Panic disorder and generalised anxiety disorder**

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In this study treatment was offered for two anxiety disorders rather than one. Arguments in favour of this decision were that they are the most prevalent anxiety disorders in primary care (Regier et al, 1988; Bijl et al, 1997), that they frequently occur as co morbid disorders, and that is feasible to make an effective treatment manual for the combination of the two disorders. It can be argued that with specific manuals for each disorder higher effect sizes could be expected. However, in primary care specific diagnostic groups are usually not as clearly separated as they are in secondary care (Terluin et al, 2004). Furthermore, panic disorder (PD) and generalised anxiety disorder (GAD) are rather comparable in nature and intensity of various symptom domains, social and work related disabilities (Mavissakalian & Zamar, 2000). In this study 75 patients were included with PD without GAD, 26 with GAD without co morbid PD and 40 with both GAD and PD. No differences between these subgroups emerged on pre-treatment characteristics, on symptom severity or dropout rate and no differences were found in treatment effect. Consequently, the lumping together of these disorder in future studies seems justifiable.

## **Comorbidity**

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As the aim of the project was to study effectiveness rather than efficacy, inclusion was not limited to pure PD or GAD, but comorbidity was allowed as long as these anxiety disorders could be considered as the primary diagnosis. Clinical relevance of efficacy studies is as a rule limited because only a small segment of the patients seen in clinical practice is enrolled. Patient selection in this study is a better reflection of anxiety disorder patients seen in primary care and selected by their GP, while at the same time strict diagnostic criteria with SCID-IV are available. Clinicians often point at the problem of translating the results of an RCT to their daily practice. They state that they are confronted only rarely with the kind of “pure” patients usually selected for these RCT’s. Recently, this criticism has been confirmed by a study which sought to determine whether patients with a current major depression participating in antidepressants efficacy trials are representative of depressive patients in the real world. This seemed not to be the case: only a small subset of patients (about 14%) with a strict clinical profile qualified for efficacy trials, which severely restricts the external validity of the results. Although this study dealt with efficacy trials of treatment of depression, its results can well be extended to the same kind of trials in other areas of psychiatry (Zimmerman et

al, 2002). We chose to increase the generalisability of our results by including patients with a comorbid diagnosis of a mood, anxiety, somatoform disorder or substance dependence.

## Treatment effects

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For the researchers it was a surprising finding that the three treatment conditions, Manual, Guidelines and CBT had an equal outcome. Lack of power is one possible explanation of negative findings in comparative outcome studies. Although the total inclusion was lower than planned, lack of power is not the best explanation for our findings. A considerably larger inclusion of patients might have shown statistically significant differences in outcome, but then clinical significance would have been very dubious.

Most unexpected was that CBT delivered by experienced therapists in a specialized outpatients clinic failed to show better results than the two primary care interventions which are considerably less time intensive and need less expertise. In terms of effect size, results obtained by CBT were at the lower end of the range of effect sizes found in other studies with CBT, but not outside that range. There are no reasons to assume that the therapists put in less of an effort for this study, so other explanations must be considered. One possible explanation could be that there was "less room for improvement" due to the assumption that the primary care patients had a lower level of symptoms compared to the patients usually treated in secondary care, symptom improvement must necessarily be more modest. Another explanation was the observation that a rather high number of patients declined to participate in treatment at the Psychiatric Outpatient Clinic, dropped out of CBT or failed to complete the twelve sessions of CBT that were planned. Several patients mentioned that the therapy they were offered was rather more intensive than they had wished for and involved more time than they were willing to devote. Apparently, their anxiety disorder was less of a burden than for most patients usually seen in specialized care for whom CBT is designed.

Of course, these findings fit very well with the Goldberg and Huxley (1992) model of filters operating in mental health: only patients with higher levels of psychopathology tend to be referred from primary to secondary care.

No data were available on the effectiveness of the Guidelines, therefore it was not possible to make a prediction about its effectiveness compared to the other treatment modalities. Nonetheless, it was a surprise that the Guidelines did as well as it did. The fact that fewer patients were referred to the Guidelines, and fewer

GP's made referrals to the study deserves some comment. It was mentioned already that some GP's expressed disappointment at being randomised to the Guideline condition rather than the Manual and some appear to have lost interest in the study altogether. It may be that those GP's remaining in the study in the Guidelines group had a more than average interest or proclivity in applying the Guidelines, and being a positive selection, they might have obtained better results. As the Guidelines is a "package" rather than a single intervention, it is not possible to decide what made the Guidelines effective. Almost half of the patients treated in the Guidelines group received either medication or referral, so one can speculate that these are important elements for its effectiveness. This study demonstrates that several GP's seem to have little enthusiasm for the Guidelines, but others appear to be able to manage anxious patients very well by applying the Guidelines.

The guided self-help treatment also proved to be an effective intervention. It was found to be feasible for GP's, apparently generating more interest and enthusiasm than the Guidelines. This of course may be a temporary phenomenon, due to its novelty. However, as the Manual contained practically useful elements such as the psycho-education, the relaxation tape, the explanation of cognitive principles and exposure, it is not surprising that GP's appreciated the Manual as a useful aid in the management of anxious patients.

The improvement in all conditions was maintained on the longer term. For CBT this was no surprise, since it has been demonstrated repeatedly that the results of CBT are usually lasting and even further improvement after treatment may occur. Apparently, both the Manual and the Guidelines also contained the elements that contribute to this stabilising effect.

Strictly speaking, we have no certainty that the improvement noted was really due to the interventions. For this we should have needed a no-treatment group that would reveal the natural course of the disorders. Not only is this hard to achieve in a primary care study, it would also have burdened the design. In secondary care it is well documented that anxiety disorders tend to remain chronic, with little spontaneous improvement. This may be less true of anxiety disorders in the general population and in primary care, although clear data are lacking (Wittchen, 1988; Yonkers et al, 1996). A certain amount of spontaneous recovery, especially on the long term is to be expected. However, this would not have reached the level of improvement seen in this study.

Rather than a no-treatment condition, we chose for a Treatment as Usual in the form of the Guidelines. We do not know to what extent this is really the treatment that is usually applied, since the systematic implementation of the Guideline has

yet to be started. But as the Guideline contains a wide scope of possible interventions, it is reasonable to assume that Usual Practice will most often be within the limits of the Guidelines.

## **Implications for Patient Care**

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The results of the present study strongly support the existing practice of referring only a selection of anxiety disorder patients to specialised secondary care. No superior results would be achieved if all anxiety disorder patients would receive CBT as offered in specialised institutions. For anxiety disorders, this study supports the rationality of the Goldberg and Huxley Filter model for delivery of care.

This study also supports the position that evidence based treatments that have been developed and tested in secondary care should not be exported without modifications to primary care. Rather, less time intensive and more easy to deliver formats should be developed, a process that is already under way in for example Problem Solving Therapy (Wilkinson & Mynors-Wallis, 1994). This means that interdisciplinary Guidelines as recently developed in the Netherlands should have the option of separate recommendations for primary and secondary care.

On the basis of this study, it can also be recommended to include guided self-help treatment in future Guidelines for General Practice. The guided self-help treatment may be a concrete way to support the GP in delivering elements that are part of the Guidelines that are otherwise time consuming, such as the explanation of cognitive principles. This would not entail a superior effect, but would rather contribute to feasibility. The present study suggests that the reception of this addition among GP's would not be negative. The guidance that is part of the treatment could also be delivered by other primary care workers than the GP, such as nurses or social workers.

## **Suggestions for future research**

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In future studies on course and treatment outcome of anxiety disorders it would be wise to treat primary care and secondary care patients as separate populations. Results from an unspecified mix of patients might rather add to confusion than to clarification. However, this recommendation will be harder to follow in countries where the Health Care System lacks clear boundaries between primary and secondary care.

At this point it is not clear whether comorbidity with depression would suggest another course. This should be a point further studies

The model of guided self-help treatment could be studied for other disorders such as depression or somatoform disorder.

Another modality of interest is that of the computer assisted programs. Several initiatives have been deployed and show interesting effects (Schneider et al, 2005). Both guided self-help treatment and computer assisted treatment could become part of an evidence based stepped care program in primary care. However, this implies that the current trend of supporting the GP with other disciplines is continued.

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# Samenvatting

## Toepasbaarheid en effectiviteit van behandeling voor angststoornissen in de eerste lijn

Dit proefschrift heeft als onderwerp de toepasbaarheid en effectiviteit van een zelfhulpbehandeling met begeleiding door de huisarts (begeleide zelfhulp) bij patiënten met paniekstoornis met of zonder agorafobie (PA) en/of gegeneraliseerde angststoornis (GAS) in de eerste lijn. Een vergelijking werd gemaakt met de standaardbehandeling in de eerste lijn (NHG - standaard angststoornissen: NHG) en de 'gouden standaard' in de tweede lijn (cognitieve gedragstherapie: CGT).

Hoofdstuk 1 gaat in op het klinische beeld, diagnostiek, voorkomen (epidemiologie), herkenning in de eerste lijn en gelijktijdig voorkomen met andere aandoeningen die patiënten met PA en GAS vaak hebben (co-morbiditeit). Vervolgens worden de NHG, CGT en de begeleide zelfhulp besproken. Tot slot van dit hoofdstuk worden de onderzoeksvragen van het proefschrift uiteengezet.

Uit onderzoek blijkt dat er veel patiënten voorkomen met angststoornissen. PA en GAS komen het meest frequent voor. Aangezien deze aandoeningen gepaard gaan met veel lichamelijke klachten, maken patiënten met PA en GAS zich vaak zorgen om hun lichamelijke gezondheid. Daardoor gaan zij vaak naar hun huisarts om geruststelling te krijgen. De huisarts probeert de patiënten gerust te stellen door laboratoriumonderzoek of lichamelijk onderzoek te laten uitvoeren of door te verwijzen naar een medisch specialist.

Wanneer de lichamelijke klachten niet herkend worden als behorend bij PA of GAS blijven deze klachten bestaan en krijgen patiënten geen behandeling voor hun angstklachten. Dat is jammer, omdat uit onderzoek is gebleken dat PA en GAS kunnen verbeteren met een psychologische behandeling, cognitieve

gedragstherapie genaamd. Deze behandeling is meestal niet toe te passen door de huisarts vanwege de intensiteit.

De NHG -standaard angststoornissen is tot op heden niet onderzocht op effectiviteit. Ook lijkt de toepasbaarheid ervan moeilijk, omdat de huisarts volgens de Standaard simpele cognitieve gedragstherapie moet uitvoeren. In dit onderzoek willen we aandacht vestigen op dit probleem en uitzoeken of een door ons ontwikkelde zelfhulpbehandeling effectief voor PA en GAS toepasbaar is bij de behandeling van deze aandoeningen in de eerste lijn. Uit de literatuur blijkt dat zelfhulpbehandelingen effectief kunnen zijn in de eerste lijn. Tevens blijkt dat begeleiding van zo'n zelfhulpbehandeling door een behandelaar (de huisarts bijvoorbeeld) deelname aan de behandeling verhoogt en het effect mogelijk groter wordt. Daarom kozen we ervoor om begeleiding door de huisarts toe te voegen aan de zelfhulpbehandeling.

Het proefschrift bestaat uit (i) een literatuuronderzoek naar het effect van in ander onderzoek geëvalueerde zelfhulpbehandelingen, (ii) een pilot studie naar de effectiviteit en toepasbaarheid van de begeleide zelfhulp, (iii) een randomised controlled trial (RCT) waarin de effectiviteit van deze begeleide zelfhulp vergeleken wordt met de effectiviteit van de NHG Standaard angststoornissen en cognitieve gedragstherapie uitgevoerd in de tweede lijn en (iv) de invloed van bijkomende stoornissen op de uitkomst van de behandelingen die werden onderzocht in de RCT.

Hoofdstuk 2 is een literatuuroverzicht van studies naar de effectiviteit van zelfhulpbehandeling bij patiënten met angststoornissen in de eerste lijn tussen 1963 en 2003. Zes geïdentificeerde gerandomiseerde studies werden vergeleken op uitkomst en gecodeerd op kwaliteit. Er was een verschil in methodologische kwaliteit, gebruikte meetinstrumenten en het aantal patiënten dat meedeed in de studie. Ondanks deze verschillen waren globale bevindingen dat zelfhulp een effectieve behandelingsmogelijkheid is bij patiënten met angststoornissen in de eerste lijn. Tevens vonden we dat hoe meer tijd er besteed werd aan begeleiding van het gebruik van de zelfhulphandleiding, hoe groter het effect van de behandeling was. Er bleken geen gegevens te zijn gepubliceerd over de toepasbaarheid en kosteneffectiviteit van zelfhulpbehandelingen.

In hoofdstuk 3 wordt het effect en de toepasbaarheid van de nieuw ontwikkelde zelfhulpbehandeling met begeleiding in een pilot studie met 5 geselecteerde eerstelijns patiënten met PA en/of GAS onderzocht. De begeleide zelfhulpbehandeling wordt gedetailleerd beschreven. Kort samengevat gaat het om een handleiding die is geschreven onder supervisie van twee ervaren

gedragstherapeuten. Eerder verschenen Engelstalige zelfhulpboeken voor patiënten met paniekstoornis, vermijding en gegeneraliseerde angststoornis. Ook werd eerder een zelfhulphandleiding ontwikkeld voor sociale fobie.

De zelfhulphandleiding bestaat uit een introductie, uitleg over angst, cognitieve technieken, ontspanningsoefeningen en oefenen in het echte leven. De patiënt wordt geadviseerd de behandeling over 12 weken te spreiden. Aan het eind van ieder hoofdstuk staan een aantal vragen over het voorgaande zodat de patiënt zelf kan controleren of hij de stof begrepen heeft. Tevens werd de patiënt geadviseerd de behandeling niet alleen te doen, maar een helper te zoeken. Met een folder over wat er van diegene verwacht wordt kon de patiënt een vriend of familielid vragen. Bij de handleiding hoort een geluidsopname van ontspanningsoefeningen, een registratieboek, een oefenboek en een boek met antwoorden op de vragen die na ieder hoofdstuk gesteld werden.

De zelfhulphandleiding werd begeleid door de huisarts in 5 consulten die over 12 weken verspreid werden. De begeleiding bestond uit het beantwoorden van vragen, het bespreken van de voortgang en het motiveren om door te gaan. In de pilot studie werd het effect geëvalueerd door middel van zelfrapportage vragenlijsten die voorafgaande en na afloop van de behandeling werden ingevuld door de patiënten. De meeste patiënten verbeterden gedurende de behandelperiode van 12 weken. Twee patiënten 'genazen' volgens de criteria van Jacobson en Truax. Geconcludeerd werd dat begeleide zelfhulp een effectieve behandelmogelijkheid kan zijn in de behandeling van PA en GAS in de eerste lijn. Deze conclusie kan echter pas getrokken worden nadat het effect van deze zelfhulpbehandeling in een gecontroleerde studie onderzocht is.

In hoofdstuk 4 wordt de hoofdstudie van dit proefschrift besproken. Doel van deze gerandomiseerde gecontroleerde studie is de effecten van begeleide zelfhulp, de standaard angststoornissen van het Nederlands Huisarts Genootschap en cognitieve gedragstherapie met elkaar te vergelijken. De behandelingen duurden 12 weken, waarna de patiënten bij 3 en 9 maanden vervolgd werden. De eerste twee behandelingen werden door 46 huisartsen uitgevoerd, die gerandomiseerd toegewezen werden voor een van deze behandelingen. CGT werd uitgevoerd door ervaren cognitieve gedragstherapeuten op de angstpolikliniek van GGZ-Buitenamstel. Honderdvier en vijftig patiënten werden gerandomiseerd toegewezen aan een van de drie behandelingen. De uitkomst werd gemeten op de STAI-state, een meetinstrument waar mate van angst mee gemeten wordt. Alle drie de behandelingen gaven verbetering van de angstklachten. Uit de vervolgmomenten bleek dat dit effect behouden bleef. De gemeten verbetering

verschilde niet tussen de behandelingen. De toepasbaarheid van de NHG-standaard voor de eerste lijn bleek echter minder groot dan die van de begeleide zelfhulp. Geconcludeerd werd dat huisartsen de behandeling van PA en GAS zelf kan doen. Behandeling op een psychiatrische polikliniek middels CGT geeft geen beter resultaat voor deze eerste lijnspatiënten dan de beschreven eerstelijns behandelingen (zelfhulp en de NHG-standaard). Begeleide zelfhulp lijkt gemakkelijker toepasbaar voor de huisarts dan de NHG-standaard.

In hoofdstuk 5 wordt bij 139 van de patiënten uit hoofdstuk 4 bekeken of het hebben van een andere psychische stoornis naast PA of GAS en in het bijzonder of een comorbide depressieve stoornis de verbetering van angstklachten door de behandeling beïnvloedt. Dit werd bekeken door middel van een zogeheten 'overlevingsanalyse' van Kaplan-Meier. De 139 patiënten werden ingedeeld in de groepen (i) een angststoornis (PA of GAS); (ii) een angststoornis in combinatie met andere angststoornissen en (iii) een angststoornis en een depressieve stoornis. Een patiënt wordt bij nameting of vervolgmetingen als 'genezen' beschouwd als de score op de STAI-state 34 of lager was. Deze waarde is afgeleid uit gemiddelde scores op de STAI in een groep niet-angstige proefpersonen. In de groep met depressieve klachten genazen significant minder patiënten dan in de groep met meerdere angststoornissen en de groep met één diagnose. Er was geen verschil in genezing tussen de groep met één diagnose en de groep met naast deze diagnose tevens een comorbide andere angststoornis. Geconcludeerd wordt dat het hebben van een comorbide depressieve stoornis het effect van de behandeling van de angststoornis negatief beïnvloedt. Op grond van deze resultaten zou geconcludeerd kunnen worden dat voor eerste lijnspatiënten met een PA of een GAS in combinatie met een depressieve stoornis cognitieve gedragstherapie mogelijk niet de meest aangewezen behandeling is.

In hoofdstuk 6 wordt nader ingegaan op belangrijke onderwerpen en bevindingen van voorgaande hoofdstukken. In dit hoofdstuk ligt de nadruk op algemene discussiepunten betreffende de wijze van werving, screening, keuze van angststoornis, comorbiditeit en behandeling van patiënten met angststoornissen binnen de eerste lijnsgezondheidszorg.

In deze studie is gekozen de huisartsen een centrale rol te geven. Hen werd gevraagd om patiënten te screenen en een cursus te volgen om bij 2/3 van de ingesloten patiënten de eerste lijnsbehandeling uit te voeren. Het bleek moeilijk voldoende gemotiveerde huisartsen te vinden voor deze rol. De toewijzing aan de NHG-standaard behandeling had tot gevolg dat de huisarts interesse in het onderzoek verloor, en minder patiënten insloot, waardoor de generaliseerbaarheid

van de uitkomsten verminderd zijn. In een nieuwe studie zou dit voorkomen kunnen worden door huisartsen niet de selectie te laten doen en de behandelingen te laten uitvoeren door andere eerstelijns medewerkers.

Wat betreft de screening was het opvallend dat patiënten moeite hadden met de duur van het interview. Daarnaast vond men moeilijk dat dit interview plaats vond in onze psychiatrische instelling. Het zou beter zijn geweest om een minder intensieve screening te gebruiken en deze in de eerste lijn te hebben laten plaatsvinden.

De keuze van de combinatie van paniekstoornis en gegeneraliseerde angststoornis in deze studie kon onderbouwd worden vanuit andere studies. In onze studie bleek geen verschil in resultaat te bestaan tussen de twee angststoornissen. Het includeren van patiënten met comorbide stoornissen maakt de uitkomst van deze studie generaliseerbaar naar de algemene praktijk. Tevens kon de invloed van comorbiditeit worden bestudeerd op de uitkomst van de behandeling.

Een voor ons onverwachte uitkomst was dat het effect in de RCT voor de verschillende behandelingen gelijk was. Dit suggereert dat verwijzing naar de tweede lijn alleen voor een geselecteerde groep patiënten zinvol is. Er lijkt geen extra effect te verwachten als alle patiënten met angststoornissen CGT zouden krijgen. Tevens blijkt dat CGT niet naar de eerste lijn verplaatst moet worden, maar een minder intensieve behandeling een even goed resultaat biedt.

Geconcludeerd kan worden dat laagdrempelige selectie en zorg relevant zijn voor de praktijk. Hierdoor zullen patiënten eerder herkend worden en eerder behandeling krijgen. Daardoor zal mogelijk de kans op chronische klachten of oneigenlijk gebruik van de somatische gezondheidszorg voorkomen kunnen worden. Tevens zal het door deze effectieve behandeling het ziekteverzuim en functioneren in de gezins- en sociale bezigheden verbeteren. De begeleide zelfhulp kan naast in de 1ste lijn (mogelijk als onderdeel van de NHG-standaard behandeling) ingezet te worden mogelijk ook geïntroduceerd worden in de 0de lijn. De begeleiding kan ook door een andere eerstelijnsmedewerker, als een eerste lijnpsycholoog, een sociaal-psychiatrisch verpleegkundige of maatschappelijk werker worden uitgevoerd. De toegankelijkheid is groter in de 0de en 1ste lijn doordat minder stigmatisatie van de patiënten en er zullen dus meer patiënten bereikt worden. De kosten zullen voor deze behandeling zeker lager liggen dan die in de 2de lijn. Mocht er sprake zijn van ernstigere angstklachten, dan moet gekeken worden of er sprake is van bijkomende angststoornissen of depressie en kan een intensievere behandeling meer aangewezen zijn.

De effectiviteit van een gemakkelijk uit te voeren en goedkope behandeling als de hier onderzochte zelfhulp handleiding kan een oplossing vormen voor de relatief schaarse mogelijkheid tot hulpverlening binnen de Geestelijke gezondheidszorg (GGZ). Vervolgonderzoek met deze vorm van behandelen in de eerste lijn lijkt dan ook zinvol te zijn. Er kan in dit onderzoek bijvoorbeeld ingegaan worden op de toepasbaarheid en effectiviteit van een begeleide zelfhulp voor een bredere groep patiënten, waarbij zowel angststoornissen als depressie meegenomen worden in de behandeling. Dit idee komt voort uit de bevinding dat een comorbide depressie een negatieve invloed heeft op de uitkomst van een behandeling voor PA en GAD alleen. Tevens kan onderzocht worden of discipline van de begeleider in de begeleide zelfhulp uitmaakt.

Gedacht kan worden aan het vergelijken van het effect van verpleegkundige of maatschappelijk werkende met de huisarts. Een vergelijkende studie tussen zelfhulp en medicatie lijkt daarentegen niet zinvol te zijn. Er is recent gevonden dat er geen verschil in effectiviteit bestaat tussen medicatie en psychotherapie bij milde tot matig ernstige klachten. In toekomstige studies kan ook het kosteneffectiviteits aspect van begeleide zelfhulp ten opzichte van andere behandelingen worden onderzocht. Voor zover nu onderzocht lijkt de in deze studie gevonden toepasbaarheid en effectiviteit van een begeleide zelfhulphandleiding een uitstekende oplossing te vormen voor zowel vele eerste lijnpatiënten met angststoornissen als hun huisartsen.

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## Curriculum Vitae

Christine van Boeijen was born on the 13th may 1967 in Amersfoort, the Netherlands. In 1985, after receiving undergraduate education at the Carolus Clusius College in Zwolle, The Netherlands, she started the study of medicine at the Vrije Universiteit in Amsterdam. In 1992 she graduated as a medical doctor. After one year of residency in psychiatry at the inpatient clinic for eating disorders in the Robert Fleury Stichting in Wassenaar, The Netherlands and one year of residency in psychiatry in the outpatient department for anxiety disorders of the Psychiatric Centre of Amsterdam, she started research under Prof. R. van Dyck and Prof. A.J.L.M. van Balkom in combination with the psychiatry specialisation in the same institute under Prof. W. van Tilburg. The residency of social psychiatry was taken at the outpatient department of De Gelderse Roos in Arnhem under N. de Mooij. From September 2003 she is employed as a psychiatrist at De Gelderse Roos in Ede.