PHARMACOLOGICAL AND PSYCHOLOGICAL ASPECTS OF ANXIETY MANAGEMENT IN PRIMARY CARE.

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ABSTRACT

Pilot Study :

a) 21 Generalised Anxiety Disorder (GAD) patients were treated double-blind with either diazepam or placebo for 6 weeks. This active treatment period was preceded by one-week single-blind placebo 'wash-in', and followed by two-week single-blind 'wash-out'. Results showed that diazepam used in moderate doses for 6 weeks produced anxiety recurrence and withdrawal symptoms.

b) 10 GAD patients were randomly allocated to Cognitive-Behaviour Therapy (CBT) and compared with the above diazepam and placebo groups. All treatments were balanced for degree of psychologist/patient contact. At cessation of active treatment CBT superiority was indicated. Post-Study psychotropic prescription and psychological treatment were assessed at 12 months follow-up. The CBT group had the lowest incidence of subsequent treatment interventions.

Main Study :

101 GAD patients were randomly allocated to diazepam, placebo, CBT, CBT + diazepam, and CBT + placebo, and treated over 10 weeks. Outcome measures at end of treatment and at 6 months follow-up revealed the superiority of all CBT treatments; especially CBT alone, and CBT + diazepam. Diazepam was more effective than placebo. CBT + diazepam, and diazepam groups showed no anxiety recurrence during graded withdrawal.

Secondary Study :

205 long-term benzodiazepine users were matched for age and sex with controls. Inspection of medical case notes showed that benzodiazepine users had higher rates of previous physical illness, GP attendance,and non-psychotropic drug prescription. Differences emerged between anxiolytic, hypnotic, and anxiolytic + hypnotic benzodiazepine users in age, history of physical illness, and previously prescribed medication.

Tertiary Study :

44 long-term benzodiazepine users were interviewed. The incidence of psychological ill-health and social problems was lower than expected. Patients were dependent on medication, and reported concern if their medication were to be stopped. Nevertheless 40% considered stopping benzodiazepines.

Results from the above studies are discussed in relation to clinical management of GAD, and current concerns about benzodiazepine dependence and withdrawal.

CHAPTER 1 : INTRODUCTION.

Anxiety is a ubiquitous phenomenon of everyday life (Lader 1972). Generalised Anxiety Disorder (GAD) is regarded as being the most prevalent of all anxiety states (Weissman 1985). Since the introduction of benzodiazepines in the mid 1960's they have been the pharmacological treatment of choice for all anxiety states (Greenblatt and Shader 1987), and continue to be so for the treatment of GAD (Woods and Charney 1988).

However for a number of years there has been a growing concern about the efficacy of benzodiazepines and dependency (Committee of Safety of Medicines, 1980). Short-term prescription and withdrawal from long-term use are now recommended (Committee on Safety of Medicines 1988).

Unfortunately the efficacy of benzodiazepines and their subsequent withdrawal when prescribed for the treatment for GAD in a primary care setting have not been thoroughly investigated. Furthermore, information about the characteristics, attitudes, and psychological ill health of long term benzodiazepine users is lacking.

Even the efficacy of specific psychological techniques for the management of GAD is inconclusive; reduction in anxiety is small and rarely of clinical significance (Ost 1982). As a consequence multidimensional and mixed treatment approaches have been advocated (Mathews 1985), for example, combining cognitive and behavioural approaches with progressive relaxation training. To date however

the standard pharmacological treatment for GAD has not been adequately evaluated in comparison with multidimensional psychological treatment approaches.

The current study examines a number of the issues raised above. Chapter 2 presents the historical perspective of GAD classification and definition. Problems associated with GAD differential diagnosis are discussed. Studies assessing GAD prevalence, and possible precipitating and antecedent factors are reviewed. Chapter 3 is concerned with the introduction, development, and extent of use of benzodiazepines. Studies evaluating characteristics of long term users and problems of dependency, withdrawal, and possible functional and organic impairment are evaluated. A detailed review of the studies investigating the efficacy of anxiolytic and psychological treatment is presented in Chapter 4. Chapter 5 lists the detailed aims of the studies presented in the chapters that follow.

The Pilot Study reported in Chapter 6 is divided into two sections. Firstly, a 'Controlled Comparison of Withdrawal Symptoms and Anxiety Recurrence Following Six Weeks Double-Blind Diazepam or Placebo Treatment for Generalised Anxiety Disorder in Primary Care'; and secondly, a 'Controlled Comparison of Cognitive-Behaviour Therapy, Diazepam and Placebo in the Management of Generalised Anxiety Disorder in Primary Care'. The Main Study of Chapter 7 involves 'A Controlled Comparison of the Efficacy of Diazepam, Placebo, Cognitive-Behaviour Therapy, Diazepam plus Cognitive-Behaviour Therapy, and Placebo plus Cognitive-Behaviour

Therapy in the Management of Generalised Anxiety Disorder in Primary Care'. Chapter 8 is a 'Controlled Comparison of Characteristics of Long Term Benzodiazepine Users in General Practice' and Chapter 9 follows with an assessment of 'Psychological Ill-Health and Attitude to Benzodiazepine Use and Withdrawal Among Long-Term Benzodiazepine Users'. Finally in Chapter 10 the findings of the previous studies are discussed and suggestions are made for future research.

CHAPTER 2 : NATURE OF GENERALISED ANXIETY DISORDER.

2.1 Historical Perspective

The word "anxiety" is derived from a variety of sources (Lader 1972). Firstly, from the Latin "anxietas", meaning disquiet; secondly from the Latin "angor" which refers to a sense of constriction; and thirdly, partly as a mistranslation of the German word "angst".

An anxiety state has been regarded as a cluster of symptoms based on fear, the source of which is not recognized by the patient (Miles et al 1951). According to Marks and Lader (1973) the anxiety may be chronic and sustained, but more characteristically is episodic , lasting from a few minutes to hours or days. The chief symptoms are fear, apprehension, inattention, palpitations, respiratory distress, dizziness, faintness, sweating, irritability, tremor, chest pains, feelings of impending disaster and fears of death.

Throughout history numerous terms have been given to conditions that were indistinguishable from anxiety states. The cardiovascular symptoms led to several synonyms such as "muscular exhaustion of the heart" (Hartshorne 1864). Da Costa (1871) coined the term "irritable heart" and subsequent authors referred to "Da Costa's Syndrome" (Wood 1941). During World War I "neurocirculatory asthenia" came into vogue (Oppenheimer et al 1918) followed by "cardiac neurosis" and "vasomotor neurosis"

(Schnur 1939). Over the same period other writers assumed that the symptoms were brought on by exercise and so the "effort syndrome" came into being (Lewis 1919).

The "nervous" symptoms of an anxiety state led to several other names. "Neurasthenia" or "nervous exhaustion" was an early term (Beard 1869). The term "neurosis" was itself first introduced in the medical literature by Cullen (1772). However Freud (1894) is credited with the label "anxiety neurosis", referring to a syndrome of morbid anxiety with anxious expectation as its primary symptom. As described by Freud, anxiety neurosis subsumed two forms : chronic anxiety and anxiety attacks. Freud regarded anxiety neurosis as a chronic form of generalized or free-floating anxiety that could co-exist or occur independently from a pattern of anxiety attacks "which could erupt suddenly into consciousness without being called forth by any train of thought". Yet other synonyms such as "somatisation psychogenic reaction" were introduced (Wheeler et al 1950) but failed to achieve the popularity and prominent status of "anxiety neurosis" as a diagnostic category. The Freudian notion of anxiety neurosis was taken up with such alacrity that anxiety neurosis and hysteria together accounted for all aspects of functional psychiatric illness in Osler's 1912 classic medical textbook. According to Tyrer (1984a) there was little change in the nomenclature of anxiety disorders in the ensuing years, although the delineation of depressive illness, obsessional neurosis, the affective psychoses, and personality disorders probably reclassified many patients who

might otherwise have been labelled as anxiety neurosis. This reclassification restricted the diagnosis of anxiety neurosis to a more homogeneous population. However, further divisions ensued.

Approximately thirty years ago phobic anxiety was detached from anxiety neurosis. This followed the introduction of behaviour therapy, in the form of desensitization, as a specific treatment for phobic anxiety (Wolpe 1958). The subsequent demonstration that generalised anxiety not only failed to respond to desensitization but actually hindered improvement in phobic symptoms (Marks et al 1968) emphasised the practical importance of making the diagnostic distinction between phobic states and generalised anxiety states. The process of attrition of anxiety neurosis continued with the reported efficacy of tricyclic antidepressants (Klein and Fink 1962) and monoamine-oxidase inhibitors (Klein 1964) in the management of panic symptoms and then the subsequent notion of panic disorder (PD) as distinct from generalised anxiety emerged. Tyrer (1984a), while discussing the erosion of anxiety neurosis and the development of specific diagnostic subcategories of phobic disorders and anxiety states, concluded that Generalised Anxiety Disorder alone remained the "atavistic ghost" of its anxiety neurosis predecessor.

2.2 Classification

Two major classification systems have emerged in recent times in an attempt to clarify the diagnostic confusion and multiplicity of unreconciled syndromes.

Firstly, the ninth edition of the International Classification of Diseases (ICD-9) (World Health Organisation 1978) although widely used for disease classification, has limited clinical usefulness for anxiety disorders. According to Lipschitz (1988) it is not a diagnostic manual, but rather is a compilation of diseases for the purpose of statistical reporting for morbidity and mortality. Its descriptions of diagnoses are guides for classification, rather than operational rules for assigning these diagnoses to patients (Kramer et al 1979). As a result of these constraints the ICD-9 categories have been regarded as too ambiguous and overinclusive for ICD-9 to function as a clinically useful diagnostic manual (Jablensky 1985).

Secondly, the third edition of the Diagnostic and Statistical Manual of the Mental Disorders (DSM III) of the American Psychiatric Association attempts to provide for clinical diagnoses the sort of operational criteria that determine research diagnoses by stating explicit inclusion and exclusion criteria for each category, and by supplying in its glossary operational definitions for its terminology (Lipschitz 1988).

The evolution of the present day view of anxiety can be clearly traced through the Diagnostic and Statistical Manual of Mental Disorders (DSM). In contrast to DSM III (1980), DSM I (1952) and DSM II (1968) reflect predominantly the influence of Freud, Meyer and the psychoanalytic movement in the classification of anxiety. In DSM III anxiety is no longer listed under the neuroses but emerges in its own right as Anxiety Disorders. In

fact there is no longer a separate category of neurosis or psychoneuroses, although the term "neuroses" is retained parenthetically under the subcategories as noted in Table 2.1. In DSM III there are specific listed criteria for determining the appropriate diagnosis for any given disorder. Although nowhere in DSM I or II does the contribution of the somatic component of the disorder appear, in DSM III the presence of significant physiological components is often vital to the appropriate diagnosis.

Another striking feature of DSM III is the shift from the reactive and intrapsychic models to the phenomenological model, thereby supporting the generally atheoretical approach taken in DSM III with regard to aetiology. Despite extensive field testing of the DSM III diagnostic criteria before their official adoption, some criteria have been reported to be ambiguous. Therefore all of the diagnostic criteria, plus the systematic descriptions of the various disorders were recently reviewed, and a revised version (DSM III-R; 1987) published. The studies to be presented in this thesis were initiated prior to the publication of DSM III-R and so used the definition of Generalised Anxiety Disorder (GAD) published in DSM III.

Table 2.1. Anxiety Disorders, American Psychiatric Association

PSYCHIATRIC NOMENCLATURE

DSM I (1952)	DSM II (1968)	DSM III (1980)	DSM III R (1987)
PSYCHONEUROTIC DISORDERS	NEUROSES	ANXIETY DISORDERS	ANXIETY DISORDERS
Psychoneurotic Reactions:	Neuroses :	Phobic Disorders	(OR ANXIETY AND PHOBIC
		(or Phobic Neuroses)	NEUROSES)
Anxiety reaction	Anxiety neurosis	Agoraphobia with panic	Panic disorder
Dissociative reaction	Hysterical neurosis	attacks	Panic disorder with
Conversion Reaction	- conversion type	Agoraphobia without panic	agoraphobia
Phobic Reaction	- dissociative type	attacks	Agoraphobia without
Obsessive-compulsive	Phobic Neurosis	Social phobia	history of panic disorder
reaction	Obsessive-compulsive	Simple phobia	Social Phobia
Depressive reaction	neurosis	Anxiety State (or Anxiety	Simple phobia
Psychoneurotic reaction	Neurasthenic neurosis	Neurosis)	Obsessive-compulsive
	Depersonalisation	Panic disorder	disorder
	neurosis	Generalized anxiety	Post-traumatic stress
	Hypochondriachal neurosis	disorder	disorder
	Other neuroses	Obsessive-compulsive	Generalized anxiety
	(Unspecified Neurosis)	disorder	disorder
		(or Obsessive-compulsive	Anxiety disorder not
		neurosis)	otherwise specified
		Post traumatic stress	
		disorder - acute	
		- chronic or delayed	
		Atypical anxiety disorder	

2.3 Definition

The current DSM III definition of GAD is reproduced below:

Anxiety States (or Anxiety Neuroses)

Generalised Anxiety Disorder

Differential diagnosis. Physical disorders, such as hyperthyroidism; Organic Mental Disorders, such as Caffeine Intoxication; Adjustment Disorder with Anxious Mood; Schizophrenia; Depressive Disorders; Hypochondriasis; Obsessive Compulsive Disorder; Panic Disorder.

Diagnostic Criteria.

A. Generalised, persistent anxiety is manifested by symptoms from three of the following four categories :

(1) Motor tension : shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.

(2) Autonomic hyperactivity : sweating, heart pounding or racing, cold clammy hands, dry mouth, dizziness, light headedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhoea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

(3) Apprehensive expectation : anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.

(4) Vigilance and scanning : hyperattentiveness resulting in

distractibility, difficulty in concentrating, insomnia, feeling "on edge", irritability, impatience.

B. The anxious mood has been continuous for at least one month.

C. Not due to another mental disorder, such as Depressive Disorder or Schizophrenia.

D. At least 18 years of age.

The DSM III-R criteria for GAD are somewhat more restrictive in comparison to DSM III. In particular, DSM III-R requires that at least 6 symptoms (as opposed to a minimum of 2 symptoms in DSM III) from a list of 18 symptoms covering the "motor tension", "autonomic hyperactivity" and "vigilance and scanning" sections be present. The only other substantial alteration is that "unrealistic or excessive worry (apprehensive expectation) about two or more life circumstances" be present "for a period of six months or longer, during which the person has been bothered more days than not by these concerns". In general the DSM III-R diagnosis implies that some of the symptoms of GAD be present for at least a 6-month period as opposed to the minimum 1 month recommendation of DSM III, and in addition that the cognitive component of worry and apprehensive expectation be a prerequisite for GAD diagnosis. The implications of these changes for the present study will be discussed in Chapter 10.

2.4 Differential Diagnosis

The separation of GAD and PD has produced much debate which continues with regard to DSM III-R classification. As previously mentioned the rationale for distinguishing GAD from PD is based largely on pharmacological studies (Klein and Fink 1962; Klein 1981; Zitrin et al 1983) which claim to show that generalised anxiety does not respond to drugs that are effective in reducing panic attacks. However, in DSM III and DSM III-R, patients are diagnosed as GAD if they report both chronic anxiety and panic attacks, providing the panic attacks do not occur often enough to meet the panic frequency criteria of PD. This diagnostic process reflects both the residual status of GAD and the potentially mixed nature of this anxiety state. In order to clarify such issues researchers have attempted to investigate distinctions between PD and GAD. Hoehn-Saric (1982) failed to find differences between 69 patients with PD and 64 with GAD in terms of their childhood history, social characteristics, and personality features. The major difference between the groups was in their clinical presentation. PD patients reported some somatic symptoms of anxiety more frequently than GAD patients, especially with regard to hyperventilation and cardiovascular symptoms rather than muscular and gastrointestinal symptoms. PD patients also reported more negative affects, such as depression and irritability. In an earlier study Hoehn-Saric (1981) found greater introversion in GAD patients, than in PD patients, as measured by the Eysenck Personality Inventory (Eysenck and Eysenck 1975) but he later

failed to replicate this finding (Hoehn-Saric 1982). He concluded that GAD represents a heterogeneous group of disorders which differs from PD in having less severe symptoms. In a not dissimilar study comparing 48 PD and 18 GAD patients, Anderson et al (1984) reported fewer autonomic symptoms and an earlier more gradual onset for the GAD group. They also suggested that GAD had a more chronic course yet more favourable outcome as determined by number of symptoms at interview. However they noted "these findings may have been chance differences related to small sample size". They also stated that some GAD patients reported persistent symptoms leading to secondary depression and psychiatric treatment. Rapee (1985) compared 38 PD and 48 GAD patients and concluded that PD is characterised by sudden onset around the mid to late 20's age group, and is distinguished by symptoms which are chiefly hyperventilatory in nature and which are accompanied by thoughts of serious physical or mental illness. In comparison GAD was found to be characterised by a gradual onset of somatic symptoms which are generally accompanied by a realisation that the symptoms are the result of anxiety and are harmless. These results are similar to those of Hibbert (1984) who compared the anxiety related thoughts of 8 GAD and 17 PD patients and stated that PD patients reported experiencing cognitions associated with disastrous consequences centering on the theme of personal physical harm, whereas GAD patients reported less dramatic cognitions. Hibbert (1984) explained this finding by suggesting that PD patients, in comparison to GAD patients, systematically misconstrue their

somatic experiences as dangerous in a way which is consistent with the proposals of Beck et al (1974) and findings of Butler and Mathews (1983) that anxious people overestimate subjective personal risk.

The problem of differential diagnosis has also been tackled by investigators assessing the reliability of DSM III anxiety disorders. DiNardo et al (1983) assessed 60 consecutie outpatients at an anxiety disorder clinic using a structured interview consisting of symptoms and signs defined in the DSM III. Interviews were conducted by 2 assessors. PD was found to be distinguishable from other anxiety disorders with high levels of inter rater reliability (kappa coefficients greater than .692). The only anxiety disorder that demonstrated poor diagnostic reliability was GAD (kappa coefficient = .467). GAD was the most consistently chosen alternative diagnosis , which indicated that the symptoms of GAD are commonly associated with other disorders. DiNardo et al (1983) concluded that "GAD becomes a residual category, used when the clinician has ruled out other disorders". Cameron et al (1986) compared 316 patients representing all specific DSM III anxiety disorders, except post-traumatic stress disorder, on a number of variables, including symptom profiles and demographic data. Symptom severity profiles showed both similarities and differences between anxiety disorders. PD, GAD and agoraphobia with or without panic were similar to each other and were more severely debilitating than the other disorders. Small differences between PD and GAD existed and concerned symptom

profile (especially "abdominal cramps") and age of onset. Common symptoms throughout the diagnostic categories were cognitive symptoms, cardiorespiratory symptoms and sweating, and gastrointestinal and urinary symptoms. Barlow et al (1986) classified 108 patients into the various DSM III anxiety disorder categories. Although patients with a primary diagnosis of GAD were more chronic than PD patients, most patients in each category met the DSM III criteria for GAD with the exception of simple phobics. On the basis of these data Barlow et al (1986) concluded that GAD was a residual category within the anxiety disorders, since GAD symptoms were almost always present.

In addition Barlow et al (1986) suggested that the cardinal feature of GAD was "apprehensive expectation" with "accompanying autonomic symptoms" and that patients could be characterised as "chronic worriers". Given the apparent residual nature of GAD it is hardly surprising that researchers (DiNardo et al 1983; Barlow 1985) have reported the diagnostic reliability of GAD as relatively low (kappa coefficient = .467), at a level which according to Cerny et al (1984) is respectable but nevertheless well below the reliability of other anxiety disorders. However as Cerny et al (1984) have illustrated this relatively low reliability coefficient may be due to several factors associated with DiNardo et al's (1983) study. Firstly, the small sample of patients diagnosed as GAD (N=12, or 11.1% of the sample). Secondly, 84% of patients diagnosed as agoraphobia with panic and 78.6% of those diagnosed as PD also met the diagnosis for GAD. Fifty per cent of GAD

patients also reported uncued panic attacks but at a frequency too low to meet the criteria for PD. Thirdly, 83% of the GAD patients were given at least one other diagnosis, a situation which does not enhance diagnostic clarity. Fourthly, severity ratings of the anxiety symptoms that are reportedly characteristic of GAD did not discriminate between the various anxiety disorders.

In general, the above data suggest that the symptoms defining GAD appear frequently in other anxiety disorders and that low-frequency panic attacks occur often in GAD and that GAD patients have been struggling with anxiety-related problems longer than PD patients. The ubiquity of GAD symptoms and the likelihood of additional diagnoses make the reliable classification of GAD problematic. In addition the relationship of panic to GAD has not been specified clearly, partially because the research on these DSM III and DSM III-R anxiety states is sparse. Furthermore, as suggested by Tyrer (1986) "panic is not nearly as distinct a symptom as DSM III," and by implication DSM III-R, "would have us believe".

Cerny et al (1984) have reported an alternative view that it may be heuristic to conceptualise GAD as a primary diagnostic category, whose cardinal feature is based on the focus of the apprehensive expectation, rather than as a residual disorder. In this reconceptualization the chronic worry of GAD is distinguished from the anticipatory anxiety often found in other anxiety disorder categories not only by the duration of the worry but also by its content. Accordingly GAD is diagnosed only if the

apprehensive expectation is focused on multiple life circumstances that are unrelated to anxiety anticipatory of phobic exposure or panic attack. These suggestions clarify and begin to define operationally the differences between anticipatory anxiety and chronic worry. According to Cerny et al (1984) it may well be that GAD patients who experience low frequency panic are troubled by both anticipatory anxiety and chronic worry, while those without panic struggle with chronic worry only. Such a distinction may be both practically and theoretically useful. However, it maintains the assumption that GAD symptoms are primarily cognitive and somatic in nature and fails to enquire whether a behavioural component exists. In other words, GAD is conceptualised as comprising two of the three components of Lang's (1971) Three Systems Theory. This is reflected in Barlow et al's (1984) comment that "exposure is of little or no use to those with generalised anxiety disorder .... since they avoid nothing to begin with". However, Butler et al (1987b) attempted to ascertain to what extent avoidance behaviour and situational anxiety was present in a sample of 45 GAD patients. Seventy eight per cent of the patients reported anticipatory anxiety, 80% reported some form of situational anxiety and 64% reported avoidance. Clinical observation of the same GAD patients confirmed that the reported situational anxiety and avoidance behaviour was less consistent and circumscribed than that required for a diagnosis of phobic disorder. This finding is at variance with GAD symptom profiles reported in the literature. Butler et al (1987b) reported that the

situational anxiety in GAD patients was variable, and resulted in a diffuse pattern of avoidance which contrasted with the more focussed avoidance of a smaller number of situations in phobic patients. The pattern of avoidance in GAD resembled that observed in social phobia and, according to Butler et al (1987b) was likely to require the modified form of exposure treatment developed for social phobics by Butler (1985). In the light of this latter finding the differential diagnosis and subsequent treatment of GAD may be even more problematic as the disorder appears to consist of cognitive, somatic and behavioural symptoms, with or without episodic panic attacks, the diagnosis being conferred in the absence of any other primary anxiety disorder.

2.5 Prevalence

Although its definition will significantly affect its prevalence, generalised anxiety is regarded as prevalent in the population. Dunn (1983) reported anxiety neurosis to be the most common psychiatric disorder diagnosed by general practitioners in Britain. Lader (1975), from a community survey, reported that 44% of the subjects experienced some anxiety symptoms, 31% could be classified as having subclinical neurosis, and 5% suffered enough from severe anxiety to seek treatment.

George et al (1986) found an overall prevalence rate of about 8% for GAD similar to that of Lader's (1975) treatment seeking group. Weissman (1985) reported GAD prevalence varying from 2.5 to 6.4%, making GAD the most commonly reported anxiety disorder,

occurring two to five times more frequently than PD. In general little socio-demographic data is available regarding GAD. Weissman (1985) found that GAD was more common in middle and younger aged females, in non-whites, in the unmarried, and in those from lower socioeconomic groupings.

2.6 Genetic and Family Studies

Family and twin studies have generally been concerned with the distinction between PD and GAD. In reviewing the rather sparse literature Breir et al (1985) concluded that there was strong evidence that PD, but not GAD, had high familial prevalence and genetic transmission. However, the data are at present ambiguous and inconclusive. Crowe et al (1983) found a higher degree of PD among relatives of probands with PD than among control relatives, but no difference in the prevalence of GAD. Noyes et al (1987) reported the frequency of GAD as higher among first degree relatives of probands with GAD than among relatives of control, PD, and agoraphobic probands. Also the frequency of PD was higher among relatives of probands with PD than among relatives of controls. There existed no difference in the frequency of PD among relatives of probands with PD and the relatives of GAD probands.

Findings of the above studies should be treated with caution as a number of methodological shortcomings exist with regard to group selection, subject recruitment, non-blind assessment of subjects, and the relatively small sample sizes.

Finally only one twin study has been published. Torgersen (1983)

found that monozygotic twins had a rate of PD and agoraphobia with panic attacks five times higher than that of same sex dizygotic twins. GAD however, demonstrated no evidence of genetic transmission.

2.7 Antecedents and Precipitants

In a retrospective study of 17 PD and 16 GAD subjects, Raskin et al (1982) concluded that both groups experienced a similar incidence of early loss, separation disorder in childhood, and separations or threatened separations as precipitants of anxiety. The authors also reported that anxiety related problems of separation seemed to be the main cause of symptoms in both groups. However, in the absence of a normal control group, it is difficult to evaluate the importance of early separations and separation disorder in childhood in the development of either PD or GAD. Furthermore, those with PD had a significantly higher incidence of a grossly disturbed childhood environment and previous major depressive episodes. Unfortunately given the small sample size and the unreplicated nature of the findings, these results need to be treated with caution.

In a retrospective community study of 2,902 subjects Blazer et al (1987), investigated the association between the onset of GAD and the occurrence of 19 designated life events during the preceding 12 months. Males reporting four or more life events had a risk of GAD 8.5 times that of males reporting zero to three life events. By contrast, the association between total life events and

GAD was not statistically significant for females. However, when using a more subjective measure, namely "unexpected, negative, very important events", both males and females who reported experiencing one or more such events had a threefold increase in the risk of developing GAD. As the authors note, theirs is the first paper to demonstrate such a relationship, albeit with limitations. For example, the findings indicate that the means by which one scales life events has an appreciable impact on the predictive value of these events. Furthermore it could not be determined whether GAD occurred immediately after a life event or many months afterwards. Nevertheless, despite the increasing emphasis on the biological aetiology of anxiety, this study emphasises the importance of environmental factors in the onset of anxiety disorders, and the importance of an individual's personal interpretation of the significance of life events.

2.8 Summary

The preceding chapter presents the historical perspective, classification, and definition of GAD. The heterogeneous character of GAD was reflected in the problems associated with differential diagnosis. The relatively high prevalence rate of GAD, in conjunction with uncertainty concerning aetiology and the wide variety of presenting symptoms has resulted in a wide range of therapeutic interventions. Pharmacological and psychological treatment approaches have been adopted in the management of GAD and each will be discussed in detail in the forthcoming chapters.

CHAPTER 3 : BENZODIAZEPINES

3.1 Historical Perspective

"The development of the benzodiazepines and their proliferation must be one of the landmarks of post-war clinical medicine" (Clare 1987). The benzodiazepines, initially chlordiazepoxide (Librium) and diazepam (Valium) were introduced over 25 years ago and were later followed by a large number of derivatives (Sternbach 1982). Benzodiazepines largely replaced the barbiturates because they were regarded as being more effective in alleviating anxiety, caused fewer and less severe side effects, were safer in overdosage, and because they induced liver enzymes much less, did not cause metabolic interactions with other drugs (Lader 1983). Furthermore, benzodiazepines were regarded as being less liable to induce dependence and subsequent withdrawal reactions (Greenblatt and Shader 1978). In addition to their anxiolytic properties the benzodiazepines have been used as anticonvulsants (Greenblatt et al 1981), as muscle relaxants in preparation for major surgery for childbirth (Cree et al 1973), for relief from acute dystonic spasms (Korczyn and Goldberg 1972), and during alcohol withdrawal (Sellers et al 1983). However, it was as hypnotics and anxiolytics that benzodiazepines achieved their greatest popularity (Greenblatt and Shader 1978).

3.2 Mechanism of Benzodiazepine Action

Benzodiazepines appear to interact with many neurotransmitter systems (Redmond 1983). The primary interactions are reported to be with the neurotransmitter gamma amino butyric acid (GABA) (Costa 1983). Interactions with cholinergic, serotonergic , dopaminergic, and noradrenergic systems are regarded as secondary (Tallman et al 1980). GABA receptors are widely distributed throughout the brain and are believed to mediate the principal anxiolytic, sedative, muscle relaxant, and anticonvulsant properties of the benzodiazepines (Costa 1983). There are reports suggesting the existence of endogenous benzodiazepine-like compounds (Petursson et al 1982; Clow et al 1983; Costa 1983), although the need for further work to clarify their existence and role has been advocated (Redmond 1983). Given the extremely broad range of actions of the benzodiazepines, it has been assumed that these compounds act on neural substrates for anxiety at multiple sites (Solomon 1976). However excepting the benzodiazepine / GABA receptor complex, Redmond (1983) states that there is no compelling evidence that any of the other neurotransmitter systems affected by benzodiazepines are responsible for their anxiolytic action. However the actions of the benzodiazepines are too broad to eliminate many other possibilities. It appears that further research is required to delineate the specific neurotransmitter systems involved in the action of benzodiazepine anxiolytics.

3.3 Extent of Usage

From 1965 onwards use of the relatively hazardous barbiturates began to decline while that of benzodiazepines rose steadily. In 1977 diazepam was the drug most commonly prescribed by general practitioners in the United Kingdom, accounting for 4.3% of all prescriptions (Skegg et al 1977). Furthermore, in the United Kingdom , approximately 85% of all benzodiazepines are prescribed by general practitioners (Rose 1983). In 1979 over 60,000,000 prescriptions for benzodiazepines were issued in the United States (Rosenbaum 1982). In 1980 it was estimated that 40 billion doses of benzodiazepines were taken daily throughout the world (Tyrer 1980). Within the British context 24,600,000 benzodiazepine prescriptions were issued by the family practitioner service in 1974, rising to a peak of almost 31,000,000 in 1979. By 1985 prescriptions had fallen to 26,000,000 (Taylor 1987). However when prescriptions for benzodiazepine hypnotics are separated from those classed as tranquillizers, two quite different patterns emerge. In Britain benzodiazepine hypnotic prescriptions rose steadily throughout the 1970's from under 5,000,000 at the start of the decade to 13,000,000 at the beginning of the 1980s; the 1985 estimated total standing at some 14,000,000 prescriptions. By contrast, the number of benzodiazepine tranquillizer prescriptions increased from around 10,000,000 in 1970 to a peak of 18,000,000 in 1978; the 1985 estimated total was 12,000,000 - one third down on the figure of seven years previously (Taylor 1987).

A cross-national study conducted by Balter et al (1984) provided comparable estimates of past year prevalence use (the proportion of the population who took anxiolytic/sedative medications one or more times), and the duration of use (the proportion of the population who took these medications daily for various lengths of time). Rates for past-year prevalence of use varied from 17.6% in Belgium to 7.4% in the Netherlands, with the USA and UK being 12.9% and 11.2% respectively. There was wide variation among countries in the prevalence of long-term and short-term use, but regular daily use for 3 months or less was the predominant pattern in 10 of the 11 countries surveyed. Past-year prevalence rates were much higher for women than for men in every country surveyed.

In Britain the rapid growth in benzodiazepine prescription during the early 1970s has been referred to as the "benzodiazepine bonanza" (Tyrer 1974), and led to fears of the total tranquillisation of the population (Anonymous 1973). The ubiquitous nature of anxiety and overprescription raised concern that benzodiazepines were the new "opium of the masses" (Lader 1978). However growing criticism of the levels of use and abuse of these drugs, together with concern about patient-led demand have helped create a developing trend towards reduced prescribing. It is estimated that similar trends are occurring in other countries including the USA (Hollister 1983). However significant demand for benzodiazepines in primary care still exists in Britain (Tyrer 1980).

3.4 Long- and Short-acting Benzodiazepines

As benzodiazepine usage rose the number of benzodiazepine derivatives also increased. Marks (1983a) listed a total of 31 benzodiazepine compounds available in Germany, Italy, Japan, USA and UK. The major differences between the numerous benzodiazepines lie in their relative potency and pharmacokinetic properties. The onset and duration of action after single oral dose depends largely upon the absorption rate and the rate and extent of distribution, whereas the rate and extent of accumulation during multiple dosage depends on elimination half-life and clearance (Greenblatt et al 1981). The therapeutic implications of half-life have been addressed by several authors (Cohn 1983; Straw 1983). Compounds with shorter half-lives, which are less likely to impair daytime function after a bedtime dose are more rationally prescribed as hypnotics (Solomon et al 1979; Hindmarch 1980). Conversely where anxiolytic activity is required drugs of a longer duration of action are regarded as more suitable (Lader 1976). At present there are seven benzodiazepine compounds available on National Health Service (NHS) prescription within Britain. They can be classified as having either a long (elimination half-life usually greater than 24 hours), intermediate (half-life of 5 - 24 hours), or short (half-life of less than 5 hours) duration of action. Long-acting benzodiazepines prescribed as anxiolytics include chlordiazepoxide and diazepam. Intermediate-acting benzodiazepines, some of which may be

prescribed as anxiolytics or hypnotics, include lorazepam, nitrazepam, oxazepam, and temazepam. The sole NHS available short-acting benzodiazepine hypnotic is triazolam.
Looking at anxiolytic benzodiazepine usage by substance over the period 1978 to 1985, the number of prescriptions containing long-acting compounds fell by 12,5000,000 while those containing intermediate- and short-acting compounds increased by 5,500,000 (Taylor 1987). These results represent a significant shift in the balance of anxiolytic usage towards products with shorter plasma half-lives.

3.5 Age / Sex Patterns of Usage

Within the context of basic consumption statistics the most significant consumer variables associated with prescribing benzodiazepines are age and sex.

Several of the early studies, both in the USA and Western Europe, suggested that about one in ten males and one in five females took tranquillizers or hypnotics , usually benzodiazepines, during the course of each year, two thirds of them for at least one month at a time (Lader 1978; Balter et al 1974). World wide female consumption rates are regarded as twice those of males.
It has been estimated that in Britain some 40 - 45% of benzodiazepine prescriptions are supplied to patients aged over 65 (Taylor 1987).

In Britain 70% of both benzodiazepine hypnotics and tranquillizers are dispensed to females, but the age breakdowns

differ. In the case of tranquillizers, consumption rates in females over 40 are high, and roughly equal between age groups. It is estimated that the 13 million British women aged over 40 receive almost 60% of all the benzodiazepine medicines prescribed for the British population. For hypnotics there is a more even increase in consumption with age : the five million British women aged over 65 probably consume about 40% of all benzodiazepine hypnotics prescribed, whereas the eight million aged between 40 and 65 take about 25% of the national total (Taylor 1987).

3.6 Dependency / Withdrawal

Some authors have suggested that the widespread use of benzodiazepines is largely attributable to their effectiveness (Ballenger 1984). However, others (Rickels 1981a) state that information on the extent of drug use tells us little about the appropriateness of such use. In recent years the most persistent criticism concerning benzodiazepines has focussed on the development of dependence. The existence of such dependence is suggested by a number of single and multiple case reports (see Tables 3.1 and 3.2) including double-blind studies (Tyrer et al 1981, Tyrer et al 1983). A wide range of withdrawal symptoms including anxiety, tremor, irritability, profuse sweating, insomnia, nausea, vomiting, headache, muscular pains and stiffness, and perceptual disturbances such as photophobia, paraesthesia, and hypersensitivity to pain and touch have been described (see Tables 3.1 and 3.2). More serious symptoms such as epileptic fits

(Hollister et al 1961), and psychotic reactions (Preskorn and Denner 1977) have been noted. Estimates of the numbers of long-term users who are affected by withdrawal symptoms vary widely, with reports ranging from fifteen to forty-four per cent (Tyrer et al 1983; Hallstrom and Lader 1982). Withdrawal symptoms typically emerge in the first week after stopping the drug but may develop after a reduction in dosage (Ashton 1984). The withdrawal syndrome has been reported as lasting up to three months (Anonymous 1985), but reports of withdrawal symptoms persisting for more than 6 months and in some cases for a year or more have been published (Higgitt et al 1985). Recent extensive publicity about tranquillizers has led to increased consumer demand for medical guidance about withdrawal (Lacey and Woodward 1985). Stopping benzodiazepines abruptly is regarded as more likely to lead to severe withdrawal symptoms such as fits or confusional states (Howe 1980; Tyrer et al 1981) than is graded withdrawal. As long-acting benzodiazepines are associated with less pronounced withdrawal symptoms (Tyrer et al 1983; Rickels et al 1986) several researchers recommend substituting long-acting for short-acting benzodiazepines before withdrawal is begun (Petursson and Lader 1984; Ashton 1984). However, other authors (Bowden and Fisher 1980; Laughren et al 1982) conclude that withdrawal from long-term diazepam use does not result in any rapid recurrence of anxiety or prominent withdrawal symptoms anyway, regardless of whether the withdrawal is rapid or gradual.

Table 3.1. Reports of withdrawal reaction from high dosage benzodiazepine tranquillizers.

Authors	Drug and Dose Range or Mean daily dose (mg)	Duration of drug use	No of patients studied	Main Withdrawal symptoms
Hollister et al (1961)	Chlordiazepoxide 300 -600	1 - 7 months	11	Psychosis, epileptiform convulsions insomnia, anorexia, agitation.
Slater (1966)	Chlordiazepoxide	4 years	1	Sweating, abdominal cramps, subcutaneous crawling sensations
Gordon (1967)	Diazepam 60	1 year	1	Agitation, tremor, hyperhydrosis
Preskorn and Denner (1977)	Diazepam 60-160 (+ other tranquillizers)	6 - 24 months	3	Anxiety, restlessness, tremor, organic psychosis (including auditory and visual hallucinations)
Allgulander and Borg (1978)	Chlorazepate	3 months	1	Delirium, confusion
De Bard (1979)	Diazepam 80	4 years	1	Acute organic brain syndrome (including visual hallucinations, disorientation, seizures and coma)
Miller and Neilsen (1979)	Diazepam 60-80	8 years	1	Anxiety, emotional lability, diahorrea, restlessness.
Stewart et al (1980)	Lorazepam 20	4 months	1	Disorientation, nausea, stumbling gait.
Hallstrom and Lader (1981)	Diazepam 135 (or equivalent)	3 - 14 years	4	Anxiety, sleep disturbance, intolerance to bright light and noise.

Table 3.2. Reports of withdrawal reactions from low dosage (therapeutic use) benzodiazepines

Authors	Drug and dose range or mean daily dose (mg)	Duration of drug use (mean or range)	No of patients studied	Main withdrawal symptoms
Covi et al (1973)	Chlordiazepoxide 30 - 40	5 months	39	Anxiety, tremor, anorexia, dizziness
Bant (1975)	Diazepam 30	1 - 2 years	2	Severe tremor
Vyas and Carney (1975)	Diazepam 30	3 years	1	Confusion, grand mal seizures
Rifkin et al (1976)	Diazepam 30	3 months	1	Grand mal convulsions
Dysken and Chen (1977)	Diazepam 15 - 30 (+alcohol abuse)	7 years	1	Dysphoria, disorientation, confusion, psychosis with 'hypomanic' presentation
Pevnick et al (1978)	Diazepam 30 - 45	20 months	1	Precipitous weight loss, dysphoria, tremor
Bowden and Fisher (1980)	Diazepam 32	1 - 7 years	23	(no withdrawal reactions but the suggestion of gradual anxiety recurrence)
Einarson (1980)	Lorazepam 8 - 12	1 - 6 months	4	Epileptic seizures
Howe (1980)	Lorazepam 7.5	4 - 7 years	2	Panic, nocturnal tonic and clonic seizures, myoclonic jerks.
Khan et al (1980)	Lorazepam Diazepam Oxazepam	3 - 10 years	4 2 2	Anxiety, irritability, tremor, vertigo, tinnitus, palpitations, hyperacusia, headaches
Winokur et al (1980)	Diazepam 15 - 25	6 years	1	Depersonalisation states, paresthesias, ataxia, delirious withdrawal psychoses or epileptiform crises.

(Table 3.2 Contd.)

Hallstrom and Lader (1981)	Diazepam 20 (or equivalent)	2 - 10 years	6	Anxiety, sleep disturbance, intolerance to bright light and noise
Petursson and Lader (1981)	Diazepam 10 - 30 Lorazepam 1 - 7.5 Clobazam 30	1 - 16 years	10 4 2	Anxiety, dysphoria, perceptual changes, unsteadiness, weight loss
Schopf (1981)	Various benzodiazepines	6.3 years	8	Visual sensory changes, kinesthetic disturbances, hypersensitivity and hypo-sensitivity, depersonalisation, and derealization
Tyrer et al (1981)	Diazepam 10 Lorazepam 4	3.6 years	40	Anxiety, extreme dysphoria, perceptual ataxia, hypersensitivity to sensory stimuli, retching, muscle twitching.
Laughren et al (1982)	Diazepam 17	1 - 12 years	24	(No prominent withdrawal syndrome but the suggestion of gradual anxiety recurrence)
Lader and Lader and Petursson (1983)	Diazepam 17 Other benzodiazepines	1 - 16 years	17 10	Anxiety, tension, sleep disturbance, loss of appetite, metallic taste, hypersomnia, paresthesia, sore eyes, photophobia.
Tyrer et al (1983)	Diazepam 5 - 20	3 years	41	Reduced sleep, depersonalisation, sadness, derealisation, reduced appetite, pessimism, poor concentration, indecision.
Ashton (1984)	Various benzodiazepines	3 - 22 years	12	Paresthesiae, depression, poor memory, agorophobia, panic attacks , ataxia, headache, dizziness, speech difficulty, hypersensitivity, insomnia, flushing.

(Table 3.2 Contd.)

Busto et al (1986)	Diazepam Lorazepam Oxazepam Triazolam Flurazepam Chlordiazepoxide Nitrazepam (Average daily dose = 15mg of diazepam or equivalent)		22 11 3 1 2 1 1	Persistent tinnitus, involutary movements, paresthesias, confusion, perceptual changes.
Rickels et al (1986)	Diazepam 15.2 Chlorazepate 18.2 Lorazepam 3.9 Alprazolam 2.7 Other benzodiazepines	<3 - <15 years	40 12 36 6 16	(More severe withdrawal syndrome but the suggestion of gradual anxiety recurrence).
Schweizer and Rickels (1986)	Diazepam Lorazepam Chlordiazepoxide Clorazepate Alprazolam (Average daily dose = 22mg of diazepam or equivalent)	10 years	6 4 2 2 1	(The addition of buspirone did not lessen withdrawal symptoms).

Unfortunately information on optimal withdrawal procedures is lacking - for relatively little systematic research has been done on the treatment of benzodiazepine dependence. Studies that have been published have had methodological limitations. For example, a significant number of studies investigating benzodiazepine withdrawal have selected patients who previously experienced difficulty discontinuing benzodiazepine medication (Busto et al 1986; Hallstrom and Lader 1981). However Tyrer (1984b) reported that fifty per cent of patients can cease benzodiazepine treatment without experiencing withdrawal symptoms. Other studies investigating benzodiazepine withdrawal used patients who had been maintained within recommended doses for prolonged periods prior to withdrawal (see Table 3.2) - although the recommended length of benzodiazepine treatment was only eight to ten weeks (Committee on Safety of Medicines 1980). Recommended treatment is currently only two to four weeks (Committee on the Safety of Medicines 1988). Other studies have used patients who have either been prescribed or have self-administered high doses of benzodiazepines which were well above the recommended level (see Table 3.1). In other studies up to 33% of subjects continued to indulge in concomitant "recreational drug use" during withdrawal from benzodiazepines (Rickels et al 1986). In particular Rickels et al (1986) noted that "Drugs primarily taken were marijuana, but to some extent also Quaalude, 'downers', amphetamines, LSD and cocaine", thereby making interpretation of their data rather difficult.

With the exception of two papers (Fontaine et al 1984; Murphy et al 1984) controlled studies of benzodiazepine withdrawal after the administration of short-term therapeutic doses are lacking. Fontaine et al (1984) reported the results of a "double-blind, placebo controlled study of four weeks of benzodiazepine" (diazepam or bromazepam) treatment followed by 3 weeks placebo substitution. Sixteen patients were withdrawn from benzodiazepines abruptly, fourteen were withdrawn gradually, and thirteen received placebo throughout. Patients whose benzodiazepine was withdrawn abruptly exhibited 'rebound' anxiety evidenced by increases of 10% or more above baseline total scores on both the Hamilton Rating Scale for Anxiety (Hamilton 1959) and a Self Rating Symptom Scale (Guy 1976). However there were no cases of rebound anxiety in patients whose benzodiazepine was withdrawn gradually. In addition Fontaine et al (1984) reported that fewer cases of rebound anxiety were seen in patients who had received a long half-life benzodiazepine, namely diazepam. The most common withdrawal symptoms for both gradual and abrupt withdrawal groups included insomnia, gastric problems, tremors, agitation, fearfulness, and muscle spasms. Fontaine et al (1984) reported this study to illustrate rebound anxiety and withdrawal symptoms after only four weeks benzodiazepine treatment. However, there exists one major flaw that negates such a claim. They noted that "immediately before entering the 1 week" placebo run-in period prior to double-blind randomisation "20 patients had been treated continuously with benzodiazepines (the majority with diazepam) for more than 1 year,

17 for 3 months to 1 year, and 5 for less than 6 months; 6 were untreated". It therefore appears wholly unwarranted to claim that this study investigates rebound anxiety and withdrawal symptoms after "4 weeks of benzodiazepine treatment" given that 87.5% patients had been receiving long-term drug therapy prior to study inclusion. Fontaine et al (1984) assume that a one week placebo run-in period in between long-term benzodiazepine consumption and the start of the double-blind study was adequate. This approach has been strongly criticised by Tyrer and Owen (1984) who note that

> "A matter for concern in current drug trials is the relative rarity of studies in which patients have been on no drug treatment at the time of assessment. Most patients are taking a benzodiazepine drug at this time and it is often considered appropriate to have a washout period of one week before starting a drug trial. This period is not adequate to allow for the resolution of symptoms that are at least partly a consequence of benzodiazepine withdrawal (Petursson and Lader 1981; Tyrer et al 1981; Tyrer et al 1983) and may be preferentially helped by a trial benzodiazepine drug because of cross tolerance between members of the series". (Tyrer and Owen 1984, p.78)

In addition it has been argued that the longer the course of benzodiazepine treatment the greater the dependency and the more marked the withdrawal symptoms (Marks 1983a). So Fontaine et al's

(1984) paper reportedly presenting withdrawal results after 4 weeks benzodiazepine treatment is in fact presenting withdrawal results after a far longer period. It is unlikely that symptoms of withdrawal would have been ameliorated in the one week placebo run-in period given the reports that withdrawal effects may last up to 6 - 12 months following the cessation of treatment (Higgitt et al 1985) and that active metabolites of long-acting benzodiazepine may persist in patients for as long as 200 hours after benzodiazepine treatment is ended (Cohn 1983). In summary Fontaine et al's (1984) paper does <u>not</u> assess withdrawal after 4 weeks benzodiazepine treatment.

Murphy et al (1984) reported the results of forty patients equally divided between four groups and receiving either diazepam or buspirone in flexible dosage for a period of either 6 or 12 weeks, followed by placebo substitution up to a total study duration period of 14 weeks. Patients were seen fortnightly for the 14 weeks. At each assessment the investigators completed the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al 1978). Withdrawal of diazepam at 6 weeks from a mean daily dose of 11.4 mg produced a significant increase in CPRS symptoms with a subsequent fall over 4 weeks. A non-significant increase in CPRS symptoms occurred on withdrawal after 12 weeks of diazepam treatment, "although this was not as striking as the increase after withdrawal of diazepam after 6 weeks". (There was no significant increase in CPRS symptoms after withdrawal from 6 or 12 weeks buspirone treatment). Murphy et al (1984) noted that it was

difficult to be sure whether the CPRS increase in symptoms after stopping diazepam represented true withdrawal (indicative of pharmacological dependence) or a return of pre-existing anxiety. However they concluded that the symptoms exhibited after stopping diazepam constituted true pharmacological dependence as they were absent after abrupt withdrawal from buspirone - " a finding that contradicts the argument that such symptoms are a return to the pre-drug state". Unfortunately this study has a number of shortcomings. Firstly, there is no mention of patient diagnosis, inclusion and exclusion criteria. Secondly, there is no information concerning previous history of benzodiazepine treatment or drug status in the period immediately prior to study inclusion. Thirdly there is no actual assessment of withdrawal symptoms; the increase in CPRS following abrupt termination of 6 weeks diazepam treatment was regarded as synonymous with the experience of withdrawal symptoms. Fourthly, there is no discussion as to why there should be a significant increase of CPRS (indicative of withdrawal symptoms) after 6 weeks diazepam treatment but not after 12 weeks diazepam treatment.

It therefore appears that these two controlled studies of benzodiazepine withdrawal after administration of short-term therapeutic doses are methodologically inadequate. Furthermore, despite most anxiety disorders being treated in primary care (Shepherd et al 1966), and less than ten percent being referred to psychiatrists in the United Kingdom (Goldberg and Huxley 1980), studies of anxiolytic efficacy and subsequent withdrawal hitherto

have been largely based on skewed psychiatric outpatient groups (Greenblatt and Shader 1974). These patients, are therefore an atypical sample (Tyrer and Owen 1984).

The lack of adequately controlled studies investigating the efficacy and subsequent withdrawal from short-term benzodiazepine treatment, at the recommended dosage for GAD, in a primary care setting, with patients who had not recently used or been dependent on minor tranquillizers, suggested the need for research in this neglected area.

3.7 Functional / Organic Impairment

In addition to increased concern about the volume of prescribed benzodiazepines (Tyrer 1980) and associated dependency and withdrawal phenomena (Schopf 1983), there has been a growing number of reports indicating that benzodiazepine treatment may be associated with impairment of cognitive and psychomotor functioning (Kleinknecht and Donaldson 1975; Hendler et al 1980; Hindmarch 1980; Johnson and Chernik 1982; Ghoneim et al 1984), including driving performance (De Gier and Nelemans 1981; Moskowitz and Smiley 1982), traffic accidents (Bø et al 1974), and amnesia (Dundee and Pandit 1972; Wolkowitz et al 1987). Furthermore enlargement of cerebrospinal fluid spaces in low-dose (Lader et al 1984) and high-dose (Schmauss and Kreig 1987) long-term benzodiazepine users has been reported. Specific problems of benzodiazepine anxiolytics in relation to the elderly have also been noted, for example, increased risks of falling (Linnola and

Ellinwood 1982). Disadvantages are also associated with the long-term use of benzodiazepine hypnotics in the elderly, such as confusional states (Evans and Jarvis 1972), increased daytime anxiety (Morgan and Oswald 1982), rebound insomnia (Oswald et al 1979), impaired daytime psychomotor performance (Morgan 1985), and dependence (Higgit et al 1985). The type of benzodiazepine hypnotic influences the manifestation of side effects. Long-acting drugs are more likely to accumulate and disrupt daytime activities (Morgan 1985), while very short-acting drugs produce an earlier and more severe rebound on withdrawal (Adam et al 1984).

With regard to cognitive and psychomotor impairment associated with benzodiazepine anxiolytics, research has usually been conducted on patients who have recently been prescribed benzodiazepines or on normal subjects after single doses (Linnoila and Ellinwood 1982). However Golombok et al (1988) report that high-dose, long-term benzodiazepine users perform poorly on tasks involving visual-spatial ability and sustained attention and this is consistent with deficits in posterior cortical cognitive function. Unfortunately there are few studies investigating cognitive and psychomotor performance during withdrawal from long-term benzodiazepine treatment (Lader and Petursson 1983). Petursson et al (1983) attempted to assess psychological functioning in patients following long-term benzodiazepine treatment and then during subsequent withdrawal. They reported long-term benzodiazepine use as having a differential impact on psychological performance, namely that cognitive skills such as

attention, vigilance, and pure motor speed were not adversely affected whereas tasks requiring combined use of sensory and fine motor skills may be permanently impaired. Unfortunately Petursson et al's (1983) results are difficult to interpret due to the confounding impact of practice effects and heightened anxiety levels on test performance. Conversely Sakol and Power (1988) using recently-developed computerised tests, which are less prone to practice effects, suggest that cognitive skills such as attention, vigilance and speed of information processing are adversely affected by prolonged use of benzodiazepine anxiolytics, whereas motor skills such as motor speed are not. Additionally, during graded withdrawal from long-term benzodiazepine use when anxiety levels remain constant, Sakol and Power (1988) report encouraging improvements in cognitive performance. In summary it appears that long-term benzodiazepine users are at risk of functional and possibly organic impairment, although replication of the relatively small number of studies in this area is required, and more attention should be directed towards investigating whether possible impairments are reversible or permanent.

3.8 Characteristics of Long-Term Benzodiazepine Users in General Practice.

The available data regarding extent of benzodiazepine use in general and in specific age and sex groups cited earlier (3.3, 3.5) fail to provide detailed information on the prevalence of long-term use in the community, and the characteristics of long-term users.

Since the mid-1970s there has been a decrease in the prescribing of benzodiazepines in most of Western Europe and the USA (Marks 1983a), the exception being Italy (Williams et al 1986). The prime factor in this decrease is most likely to have been a reduction in new prescribing (ie. a decreasing rate of incident benzodiazepine use) rather than the wholesale discontinuation of treatment by long-term consumers (Williams 1987). This suggests that there is a cohort of long-term benzodiazepine users, created during the "hayday" of benzodiazepine popularity in the mid 1970s, from which members will slowly be lost (a small proportion will discontinue treatment, others will die), and to which few new members will be recruited, since a reduction in new prescribing will inevitably lead to fewer people becoming long-term users (Williams 1987).

Given the problems of possible dependency, withdrawal, and functional and organic impairment it would seem important that the characteristics of long-term benzodiazepine users be identified in order that appropriate clinical management strategies be designed and implemented. User characteristics may be considered as predisposing to long-term use ; alternatively they may be regarded as characteristics which mitigate against discontinuation of treatment, or a combination of both aspects.

A number of studies have investigated various features of "psychotropic" drug users. Woodcock (1970) carried out a retrospective analysis of the medical records of 20 general practitioners, and indicated that in 1967 2.8% of patients had been

receiving a daily dosage of a psychotropic drug for at least one year. Four-fifths of these long-term consumers were aged 40 or over, and three quarters were women. Parish (1971) in a retrospective case note survey of the work of 48 Birmingham general practitioners, with a total list size of 13,259 patients, reported that 12.6% of the population had been prescribed psychotropic drugs during a one year prevalence period; representing 17.1% of females and 8% of males. Approximately 1.9 per cent of the population were prescribed a psychotropic continuously for a period of one year or more. Eighty-three per cent of patients on prolonged therapy were over the age of 40 years, and 54% of them were women over the age of 45 years. Skegg et al (1977) reported the one year prevalence of psychotropic prescribing by 19 general practitioners to a population of 36,280. During the year 9.7% of males and 21.0% of females received at least one psychotropic drug. In every age group a higher proportion of females than males received psychotropic drugs. There was a sharp increase with age in the proportion of patients receiving psychotropics. Among women it was notably high in the 'middle aged' (33.0%) but the highest proportion was found at 75 years or older (37.7%). Cooperstock (1976;1978) analysed data based on the computerised records of a prescription insurance agency in southern Ontario, and reported consistently higher proportions of female psychotropic users than male users (18% of males received one or more prescriptions for a psychotropic drug in 1970-71, compared with almost 31% of females in that year, while in 1973-74 the proportions were 14.5% and

almost 24% respectively). In addition, more females than males in each period received multiple prescriptions. Mellinger et al (1978) reported results from a cross-sectional nationwide survey of 2,552 adults in the USA. 'Regular' psychotropic drug users (defined as anyone who had used psychotropic drugs during the past year, and who also at some time had used the same drug daily or almost daily for two months or longer) were compared with those who had used psychotropic drugs anytime in the year prior to interview. Both measures of psychotherapeutic drug use were "clearly and strongly related to level of psychic distress" as assessed by a shortened version of the Hopkins Symptom Checklist (HSCL) (Derogatis et al 1974). Mellinger et al (1978) concluded that their findings suggested an "illness behaviour model" for the use of psychotropics in outpatient practice, lending little support to a "self-indulgent consumer" interpretation.

Murray et al (1981) from a survey designed primarily to investigate the effects of aircraft noise on health in West London in 1977, reported the 2 week prevalence of drug consumption in a sample of 5,904 people living within an area close to Heathrow Airport, as 10.9%. For every age group the rate of psychotropic drug consumption was twice as high in women as in men. For both sexes the proportion of drug users increased with "worsening self-assessment of health". The relationship between General Health Questionnaire (GHQ) 30 - item (Goldberg 1972) score, drug consumption, and sex (ignoring the effect of age) was analysed. They reported that "17% of the male high GHQ scores and 27% of the

female high scorers consumed psychotropic drugs. In contrast to these figures, only 5% of the male and 10% of the female low GHQ scores consumed these drugs". Murray (1981) conducted a postal survey of 261 (presumably female) "Womans Own" magazine readers, 183 of whom were classified as "present" psychotropic users and 78 as "past" psychotropic users. Murray (1981) reported a high prevalence of self-reported psychiatric symptoms among both present users (83%) and past users (55%), as measured by the 30-Item Symptom Rating Test (Kellner and Sheffield 1973). Widespread physical impairment as measured by a modified verison of the Belloc Physical Status Inventory (Belloc et al 1971) was also noted.

Williams et al (1982) reported a longitudinal study of 153 (95 females; 58 males) general practice patients beginning a new course of psychotropic drug treatment. The group of patients was characterised by high physical morbidity at time of prescribing. Twenty-three (40%) of the males and 34 (36%) of the females had a physical illness diagnosed by the GPs. Depression was cited as the most common psychological complaint of females, whereas it was sleep disturbance in males. For the majority of patients psychotropic drug treatment was short-term. Approximately 20% were still receiving psychotropic drugs six months later, and this prolonged treatment was associated with increased age, previous psychotropic drug use, higher levels of psychological morbidity at the inception of treatment, and for the women only, with social problems as perceived by the GPs. The presence of physical illness was not related to the duration of psychotropic treatment

(Williams 1983).

More recently Catalan et al (1988) identified the 3.6% (males = 83; females = 235; total n = 318) of patients on long-term psychotropic drugs (as defined by receiving at least one psychotropic prescription in each quarter of a 12-month period) in one general practice. Of the 318 patients 51% were aged 60 or over, as against 12% of the practice population. None of the long-term user population was aged under 30 as against 51% of the practice population. A subsample of 70 index patients was randomly selected from the 318 patients and matched for age and sex with a control group. All index and control patients were interviewd. Index patients had higher levels of psychiatric morbidity as shown by the Present State Examination (PSE) (Wing et al 1974), history of specialist psychiatric treatment, and previous drug overdoses. Apart from a higher rate of referral to general hospital outpatient clinics in the preceding 12 months "there was little evidence that index patients had more problems with physical health than controls".

Although the above studies provide some interesting information a number of methodological features limit their relevance with regard to characteristics of long-term benzodiazepine users. Firstly, all of the aforementioned studies have investigated "psychotropic drug" use in a heterogeneous group of antidepressants, major and minor tranquillizers, and hypnotics. Secondly, some of the studies also include stimulants and appetite suppressants within the "psychotropic" category (Parish 1971; Skegg

et al 1977). Thirdly, the earlier studies were conducted when the barbiturates constituted the predominant anxiolytic drug (Woodcock 1970; Parish 1971). Fourthly, the composition of the index group was often skewed (Murray 1981), and a lack of matched age and sex controls predominated, with one exception (Catalan et al 1988). Finally, none of the above studies investigated the characteristics of benzodiazepine users in particular.

Two papers by Mellinger et al (1984; 1984a) have reported characteristics associated with anxiolytic users (predominantly, but not exclusively of benzodiazepines). Three papers, by Gabe and Lipshitz-Phillips (1982), Salinsky and Dore (1987), and Rodrigo et al (1988) have investigated the features of benzodiazepine anxiolytic users alone, while Morgan et al (1988) have investigated characteristics of elderly hypnotic (mainly benzodiazepine) users.

Mellinger et al (1984; 1984a) presented results of a cross sectional 1979 survey of 3161 adults in the USA. Eleven percent (n = 387) of the total sample reported using a medically prescribed anxiolytic one or more times in the 12 months prior to the survey. Benzodiazepines accounted for 84% of the anxiolytics mentioned. Long-term use (defined as regular daily use for a year or longer) was relatively rare (n = 68) occurring among 15% of all anxiolytic users. The most common pattern of use was occasional use, never more than a day or two at a time. More than 81% of the occasional users reported using the medication on fewer than 30 days during the entire year. For 80% of the anxiolytic users, the longest daily use was less than 4 months. Comparing 68 long-term regular

users (> 12 months regular use), 319 other users (< 12 months use) and 2,774 non-users, Mellinger et al (1984; 1984a) concluded that long-term regular users tended to be older, with high levels of emotional distress, chronic somatic health problems, reported more visits to a physician, and were preponderantly female. Unfortunately the control group was not matched for age and sex. Mellinger et al (1984) only noted that "controlling for age reduced the magnitude of differences in number of health problems", and although no actual results were presented they state that the "differences remained strong". It is difficult to determine the significance of the reported differences between the three unmatched groups as how much variance the age factor may have accounted for is unknown. In addition it should be remembered that 16% of the anxiolytic group were in fact consuming non-benzodiazepine anxiolytics. Furthermore it is not known whether these American findings would apply to patients on benzodiazepines in general practice in Britain.

Gabe and Lipshitz-Phillips (1982) assessed the demographic features of 7 "high benzodiazepine users" (who had received at least 10 prescriptions, in at least 5 of the previous 10 years), 10 "intermittent benzodiazepine users" (who had prescriptions over less than 5 years and on fewer occasions),and "non-users" who had not been prescribed a benzodiazepine throughout the previous decade. All subjects were white, working-class females from an east-end of London general practice. The only sociodemographic factor that distinguished the groups was age. The "high" and "non-

users" were younger than the "intermittent" users. Although this study attempted primarily to assess "the meaning of benzodiazepine use for women patients from one general practice", it is difficult to attribute any significance to the results given the exceedingly small sample size, skewed composition, and generally poor methodology.

Salinsky and Dore (1987) from a total of approximately 6,000 patients in a north-west London general practice identified 96 long-term (> 1 year) daytime benzodiazepine users of whom 79 (82%) were aged over 45 years, and 66 (69%) over 55 years; 78 (81%) were female. Seventy-two (75%) of the long-term benzodiazepine users responded to a postal questionnaire assessing demographic features, attitudes towards, and use of tranquillizers, and assessing psychiatric morbidity by means of the Crown-Crisp Index (1979). For each benzodiazepine patient two controls matched for age and sex were selected from the practice register. Controls completed the same postal questionnaires with the exception of the benzodiazepine-related questions. Salinsky and Dore (1987) concluded that long-term benzodiazepine users had significantly higher scores for anxiety and other neurotic traits, but their personal histories showed few significant differences from those of controls. However, detailed examination of the paper indicates that a significantly larger proportion of the benzodiazepine users reported "suffering from chronic physical illness" in comparison to controls. Unfortunately this was not verified by any formal diagnostic procedure, or by case-note inspection, or analysed in

any further detail. While this is the only currently available report investigating long-term benzodiazepine users that has incorporated a matched age and sex control group, it nevertheless has a number of shortcomings. Firstly, patients were recruited from a single general practice. It is therefore difficult to generalise as the prescribing pattern of the GPs, and the sociodemographic characteristics of the patient population may not reflect the national pattern. Secondly, the sample size of the benzodiazepine group was relatively small. Thirdly, although Salinsky and Dore (1987) stated that they included only daytime long-term benzodiazepine users it appears that 42% of the benzodiazepine group were taking "sleeping tablets" as were 14% of the control group.

Rodrigo et al (1988) identified 82 long-term (> 1 year) benzodiazepine users from the 1985 age sex register of one south London general practice. These patients comprised 2.2% of the practice population. Sixty-four benzodiazepine users agreed to take part, and were interviewed at home using three 'schedules'. Firstly, patients were asked questions about their past and present use of medicines using a schedule modified by Murray (1981). Secondly, the Clinical Interview Schedule (CIS) (Goldberg et al 1970) was administered to identify and quantify psychological ill-health as well as information about self-reported physical ill-health. Thirdly, each patient was asked to complete the Kellner and Sheffield (1973) Symptom Rating Test (SRT) to measure psychological symptoms during the preceding week. Of the 64

patients interviewed 16 were male and 48 female, only 5 were under 40 years of age and 26 were 70 years or over. The median duration of treatment with benzodiazepines was 5 years, (range 1 - 25 years). Altogether nine different benzodiazepines were being prescribed, the most common being temazepam (25 patients), diazepam (14), nitrazepam (12), and lorazepam (11). Fifty-four patients completed the SRT. The proportion of patients scoring >12 on the SRT was substantially lower than that found by Murray (1981) in her self-selected sample of long-term psychotropic users, and that obtained by Williams et al (1982) in their study of new recipients of psychotropics in general practice. Thirty-four per cent of the patients (n = 22) were classified as CIS cases. Nineteen of these twenty-two cases were allotted an ICD diagnosis relating to depression, but only one patient was allotted an anxiety-related diagnosis. Just over half of the males and just over a third of the females reported a current physical illness. Gastrointestinal, musculoskeletal, and cardiovascular disorders were predominant.

While this is the most detailed published paper concerning characteristics of long-term benzodiazepine users, a number of methodological shortcomings exist. Rodrigo et al (1988) themselves note that the results are derived from one general practice "so the findings may not be generalisable to other settings". Secondly, they also note that "much of the information is based on recall and self report" although they did attempt to gain information on physical ill-health from GP records. Thirdly, they

appeared to group together benzodiazepine hypnotic and anxiolytic users. While this is acceptable in that the delineation between an anxiolytic and hypnotic is not absolute in pharmacological terms (Committee on the Review of Medicines 1980) or, with regard to how the drug is administered, it would nevertheless have been useful to note whether there existed any difference between the hypnotic and anxiolytic benzodiazepine groups. Fourthly, their sample size was relatively small. Fifthly and most importantly, they failed to include a control group matched for age and sex. This is especially important when the benzodiazepine group under study is predominantly elderly and an asssessment of the incidence of physical ill-health is being undertaken.

A number of studies representing a variety of methodologies and designs have attempted to identify characteristics of sedative-hypnotic users. Morgan (1983) in his review concluded that rates of sedative-hypnotic prescribing and / or usage tended to increase with the minimum age of the sample studied. Use of sleeping drugs is generally reported to be higher among elderly females than among elderly males (sex differences being less clearly defined among the young and middle aged). Benzodiazepine hypnotics, particularly nitrazepam and flurazepam appear to be common in all age groups, although a growing trend for the use of triazolam and temazepam (Morgan et al 1982) may have developed. More recently Morgan et al (1988) have reiterated their estimate that approximately 10 - 15% of the UK elderly population take a hypnotic each night over prolonged periods, often over five years. However the Committee

on the Review of Medicines (1980) stated that "most hypnotics tend to lose their sleep promoting properties within 3 to 14 days of continuous use", and should only be prescribed "for short periods of time and only after careful consideration", especially in the elderly.

Unfortunately a number of methodological inadequacies exist with regard to studies investigating hypnotic-sedative drug use. Firstly, virtually all studies encompass a variety of drugs under the sedative-hypnotic label, for example the amalgamation of antidepressants, barbiturates, and benzodiazepines in Morgan et al's (1988) most recent article. Secondly, much of the information is derived from hospital-based surveys, and may therefore not be representative of the bulk of prescriptions which emanate from general practice (Saltzman and Van der Kolk 1980; Christopher et al 1978). Thirdly, the relationship between physical health status and hypnotic drug use has not been thoroughly investigated (Morgan 1983), and therefore differences between the sexes in sedative-hypnotic use in the elderly may reflect differences in health status.

Cooperstock and Parnell (1982) reviewing methodologies and findings in psychotropic drug usage studies, conclude "distinctions should be made between drug types within large classes of drugs". Unfortunately this has not been adhered to in the vast amount of research to date and therefore little is known of the characteristics of long-term benzodiazepine anxiolytic and hypnotic users in comparison to matched age and sex controls.

3.9 Summary

The present chapter discussed the introduction of benzodiazepines. In addition the extent of usage, characteristics of long-term users, problems of long-term use, dependency and associated withdrawal reactions were also highlighted.

From the review three specific areas requiring further research are discernable.

Firstly, the paucity of well-controlled studies concerning the relative efficacy and subsequent withdrawal of short-term benzodiazepine treatment, at the recommended dosage, for generalised anxiety, in a primary care setting, with patients who have not recently used or been dependent on minor tranquillizers merits further investigation.

Secondly, the lack of information concerning the characteristics of long-term benzodiazepine users, from more than one general practice, in comparison to matched age and sex controls, with specific regard to differences between benzodiazepine hypnotic users, anxiolytic users, and hypnotic plus anxiolytic users requires attention.

Thirdly, there is a lack of information concerning patients' attitudes to benzodiazepine use and withdrawal among long-term benzodiazepine users.

These three issues are addressed in the studies conducted by the present author, which are presented in the following chapters.

CHAPTER 4 : ANXIOLYTIC AND PSYCHOLOGICAL TREATMENTS OF ANXIETY STATES AND GENERALISED ANXIETY DISORDER.

4.1 Anxiolytic Treatment of Anxiety States and Generalised Anxiety Disorder - Controlled Comparisons

Several reviews have surveyed clinical trials of benzodiazepines and most concur in confirming the effectiveness of this class of compounds as anxiolytics (Greenblatt and Shader 1987; Rickels et al 1978; Rosenbaum 1982). In one of the most often quoted early reviews of benzodiazepines as treatments for a wide range of anxiety disorders, Greenblatt and Shader (1978) noted "most clinicians and investigators seem to agree that benzodiazepine derivatives are more consistently effective than placebo in well controlled, short term trials of anxiolytic drug therapy". Of 25 such trials reviewed, 18 showed strong benzodiazepine - placebo differences, 4 a trend, and 3 no difference. However dissentient voices have been raised. Solomon and Hart (1978) in their more comprehensive review of 78 double-blind studies comparing benzodiazepines and placebo in a wide variety of often unspecified anxiety disorders concluded that all studies were "so poorly designed and executed as to be meaningless, the efficacy of the entire group of drugs as antianxiety agents must be questioned". Klein et al (1983) have conducted one of the most recent comprehensive reviews of the pharmacological treatments of specific anxiety disorders. They separately reviewed pharmacological treatment for obsessional-compulsive disorders,

agoraphobia with or without panic, simple and social phobias, and generalised anxiety disorder. Included in Klein et al's (1983) review of the pharmacological treatment of GAD are studies in which patients were classified simply as "anxiety neurosis " or "chronic anxiety disorders". They apparently assumed that the use of such categories is synonymous with the DSM-III GAD classification. While this may be true in some cases one cannot presume with any certainty that the diagnostic characteristics of GAD are equivalent to the more loose inclusion criteria of "anxiety states" used in many studies.

Klein et al (1983) cited 32 studies, some of which had placebo groups, in which the efficacy of at least two active drugs was compared. In none of these studies was the diagnostic characteristic of the sample described in detail. The presence or primacy of additional symptoms was not noted in most studies, although some studies reported concomitant depression. These 32 studies were organised into three groups based on drug class : 6 involved comparisons of two different types of anxiolytics; 18 compared anxiolytics and neuroleptics; and 8 compared anxiolytics and antidepressants. On the basis of their review Klein et al (1983) stated that as regards treatment outcome "remarkably few positive conclusions can be drawn". In addition they also noted that "no single drug class emerges as consistently superior to any other" in the treatment of anxiety states. However since the present study is primarily concerned with the efficacy of benzodiazepine anxiolytics, studies involving the comparison of

two or more anxiolytics in the treatment of anxiety states will be presented in more detail[1]. In addition Klein et al's (1983) review requires updating. The results of 13 papers comparing anxiolytic medication in the treatment of patients suffering from various "anxiety states", "anxiety neurosis", or "anxiety disorder" are presented in Table 4.1. Of the 13 papers, 6 were previously reviewed by Klein et al (1983). Overall most of the trials show a statistically significant superiority of benzodiazepine in comparison to placebo with no pronounced difference between anxiolytics in terms of who responds or the degree of improvement.

Klein et al (1983) identified only 4 comparative published clinical trials in which patients were specifically selected to fulfil DSM-III criteria for GAD, namely; Rickels (1981b), Feigher et al (1982), Goldberg and Finnerty (1982) and Rickels et al (1982). There has since been a further 7 recent comparative studies in which GAD patients alone comprised the subject population, namely; Lapierre et al (1982), Fontaine et al (1983), Ansseau et al (1985), Elie and Lamontagne (1984), Ceulemans et al (1985), Buchsbaum et al (1985) and Jacobson et al (1985).

Furthermore there are an additional 3 comparative studies in which formally diagnosed GAD patients have comprised part of the patient population (Chouinard et al 1982; Tyrer and Owen 1984; Dunner et al 1986). However, it is difficult to assess the impact

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[1]Although there are a number of earlier, less well controlled papers comparing the efficacy of a single anxiolytic with placebo, these will not be reviewed for the sake of brevity : see Greenblatt and Shader (1978); Solomon and Hart (1978) for reviews.

of anxiolytic treatment on GAD in these 3 studies due to the amalgamation of the various diagnostic groupings during analysis. All the above studies are presented in Table 4.2.

Solomon and Hart's (1978) previously noted scathing attack on the inadequacies in the design and implementation of benzodiazepine anxiolytic research hopefully would have prompted improvements in study methodology. Unfortunately however each of the 6 studies concerning anxiolytic treatment of GAD patients alone listed in Table 4.2 has major shortcomings.

Firstly, no study provides any follow-up data. Secondly, only one study (Rickels et al 1982) assesses patients one week after withdrawal from study medication; the remainder of the studies provide no withdrawal data. Thirdly, information concerning patients' drug status prior to study inclusion is absent in all but 6 studies, namely Fontaine et al (1983), Ansseau et al (1985), Elie and Lamontagne (1984), Ceulemans et al (1985), Buchsbaum et al (1985) and Jacobson et al (1985).

Jacobson et al (1985) stated that patients were excluded "if they were receiving any other psychotropic drugs", and Buchsbaum et al (1985) note that "all patients were off psychoactive medication for a period of 3 weeks prior to the study". Ceulemans et al (1985) stated that "six patients were being treated at the start of the trial (mainly with benzodiazepines)" but "that previous medication was stopped at the start of the trial" and "no wash-out period was observed".

Table 4.1 : Reports comparing at least 2 benzodiazepine anxiolytics in the treatment of anxiety neurosis / anxiety states

Authors	Diagnosis; N	Drug Conditions	Treatment Duration	Outcome : Evaluation Re : Differential Drug Effects
*Rickels et al 1974	anxious, neurotic outpatients, N = 154	chlormezanone chlordiazepoxide placebo	6 weeks	both drugs > placebo chlormezanone = chlordiazepoxide
Lader et al 1974	free-floating anxiety outpatients, N = 30	modazepam diazepam chlordiazepoxide amylobarbitone sodium placebo	2 - 4 weeks	all benzodiazepines > placebo, amyl. sod.
Sonne and Holm 1975	anxiety neurosis outpatients N = 30	diazepam bromazepam	3 weeks	bromazepam > diazepam
Fabre and McLendon 1979	moderate to severe psychoneurotic anxious outpatients N = 144	diazepam alprazolam placebo	4 weeks	both drugs > placebo alprazolam = diazepam
*Aden and Thein 1980	moderately or severely anxious outpatients N = 235	diazepam alprazolam placebo	4 weeks	both drugs > placebo alprazolam = diazepam
*Maletsky 1980	moderate to severe anxiety, N = 86	diazepam alprazolam placebo	4 weeks	alprazolam > diazepam diazepam = placebo alprazolam > diazepam
Cohn 1981	moderate to severe anxiety, N = 845	diazepam alprazolam placebo	4 weeks	both drugs > placebo alprazolam = diazepam
*Allin 1981	neurotic, anxious general practice patients, N = 44	diazepam chlormezanone	4 weeks	equal efficacy
*Wheatley 1982	anxious outpatients N = 131	diazepam buspirone placebo	3 weeks	both drugs > placebo buspirone = diazepam
*Goldberg and Finnerty 1982	moderate anxiety N = 129	buspirone chlorazepate	4 weeks	equal efficacy

(Table 4.1 contd)

Jacobson et al 1983	anxious outpatients, N = 144	diazepam clobazam placebo	4 weeks	both drugs > placebo diazepam = clobazam
John et al 1983	anxiety neurotic outpatients, N = 60	diazepam clobazam	6 weeks	diazepam = clobazam
Doongaji et al 1985	anxiety neurosis outpatients, N = 85	diazepam clobazam	6 weeks	diazepam = clobazam

‡ = Reviewed by Klein et al (1983)

Table 4.2 : Reports comparing the efficacy of anxiolytics in the treatment of formally diagnosed GAD.

Authors	Diagnosis; Criteria; N	Drug Conditions	Treatment Duration	Outcome ; Evidence Re ; Differential Drug Effects
*Rickels 1981b	GAD; DSM-III; N = 164	alprazolam diazepam placebo	4 weeks	both drugs > placebo alprazolam = diazepam
*Feighner et al 1982	GAD; DSM-III; N = 100	buspirone diazepam	4 weeks	buspirone = diazepam
*Goldberg and Finnerty 1982	GAD; DSM-II; N = 54	buspirone diazepam placebo	4 weeks	both drugs > placebo buspirone = diazepam
*Rickels et al 1982	GAD; DSM-III; N = 240	buspirone diazepam placebo	4 weeks	both drugs > placebo buspirone = diazepam
Lapierre et al 1982	GAD; DSM-III; N = 40	clobazam placebo	4 weeks	clobazam = diazepam
Fontaine et al 1983	GAD; DSM-III; N = 48	bromazepam diazepam placebo	4 weeks	both drugs > placebo bromazepam > diazepam
Ansseau et al 1985	GAD; RDC; N = 18	methylclonazepam lorazepam placebo	8 - 18 days	both drugs > placebo methylclonazepam > diazepam
Elie and Lamontagne 1984	GAD; DSM-III; N = 48	alprazolam diazepam	4 weeks	diazepam > alprazolam
Ceulemans et al 1985	GAD; DSM-III; N = 73	ritanserin lorazepam placebo	2 weeks	both drugs > placebo ritanserin = lorazepam
Buchsbaum et al 1985	GAD; DSM-III; N = 20	clorazepate placebo	2 weeks	clorazepate > placebo

(Table 4.2 contd)

Jacobson et al 1985	GAD; DSM-III; N = 39	buspirone diazepam placebo	4 weeks	both drugs > placebo buspirone = diazepam
Chouinard et al 1982	GAD; PD; RDC; N = 50	alprazolam placebo	8 weeks	alprazolam > placebo
Tyrer and Owen 1984	G A D ; P D ; Agoraphobia + PD; DSM-III; N = 36	buspirone diazepam placebo	3 weeks	buspirone = diazepam = placebo
Dunner et al 1986	G A D ; P D ; Agoraphobia + PD; DSM-III; N = 48	alprazolam diazepam placebo	10 weeks	both drugs > placebo diazepam = alprazolam

$ = Reviewed by Klein et al (1983)

Elie et al (1984) reported that of 48 patients, 24 were being treated with oxazepam, and thirteen with lorazepam before entering a one week single-blind washout period. However Fontaine et al (1983) stated that "immediately before entering the study 20 patients had been treated with benzodiazepines for more than 1 year; 17 for 3 months to 1 year; and 5 for less than 3 months" prior to one week placebo washout, and thereafter random allocation to bromazepam, diazepam, or placebo. Ansseau et al (1985) stated that patients were included "with a minimum 1 year history of regular daily intake of high doses of tranquillizers" with no wash-out period prior to random allocation to anxiolytics or placebo. As previously noted, Tyrer and Owen (1984) stated that rapid withdrawal from long-term benzodiazepine treatment followed by a one week placebo period is methodologically inadequate and does not allow for the resolution of symptoms that are at least partly a consequence of benzodiazepine withdrawal. Additionally withdrawal may be preferentially helped by a trial benzodiazepine drug because of cross tolerance between benzodiazepine derivatives. Thus lack of placebo efficacy in some of the above studies may be partly attributable to patients experiencing benzodiazepine withdrawal symptoms during the study period. One may only speculate as to whether the other 4 studies which failed to report details of drug status prior to study inclusion are subject to such criticism. Fourthly, although studies may produce statistically significant drug vs. placebo differences and/or reductions in anxiety rating prior to and following benzodiazepine treatment, this does not

necessarily imply significant clinical improvement. Virtually all clinical trials, including those listed in Table 4.2, use the Hamilton Anxiety Scale (HAM-A)(Hamilton 1959) as the main outcome measure. The HAM-A observer rating scale is so well established that it is employed routinely in anxiolytic studies in the USA and UK. Reductions from an initial score of between 25 to 30 at the beginning of a study to an end point of between 15 to 20 will generally produce statistically significant results. Lader (1985) in his review of double-blind placebo controlled studies published between 1977 and 1982 that used the HAM-A, stated that such reductions are the norm for those on benzodiazepine treatments (while placebo treatments tend to produce lesser reductions, with end-points between 20 to 25). In addition Lader (1985) stated that these benzodiazepine reductions on the HAM-A do not lead us to conclude that patients are "cured", as they are still experiencing clinically significant symptomatology. Furthermore Lader (1985) noted that benzodiazepines "seem less effective compared with placebo when self-ratings are used than when a trained observer rates the patient". The studies listed in Table 4.2 fit such a pattern. In particular patients' and referring physicians' ratings of degree of clinical improvement are sometimes not included (Ansseau et al 1985; Lapierre et al 1982); or patients' rating of clinical improvement is restricted to oversimplified choices, e.g. improved v. unimproved (Rickels et al 1982); or patients' and physicians' ratings of clinical improvement contradict the statistically significant results achieved on the HAM-A (Feighner

et al 1982). Feighner et al (1982) achieved statistically significant reductions on the HAM-A following anxiolytic treatment, but 57 - 60% of patients rated themselves as experiencing "no change or worse" as did 57 - 62% of the respective referring physicians.

In summary, despite the methodological limitations of the above studies, it is still widely accepted that "for GAD the benzodiazepines are the drugs of first choice" (Woods and Charney 1988), although there is no persuasive evidence that any benzodiazepine is more effective than any other (Greenblatt and Shader 1974; Klein et al 1980; Mavissakalion 1982; Rosenbaum 1982; Ballenger 1984).

Unfortunately it appears that Solomon and Hart's (1978) request for improved study methodology has not been wholly successful and there remains a need for properly controlled clinical trials of anxiolytics with particular regard to drug free status at time of study inclusion, continued assessment during withdrawal, long-term follow-up, and the use of a wider range of assessment measures including patients'and referring physicians' assessment of degree of clinical improvement/unimprovement.

4.2 Psychological Treatment of Anxiety States and Generalised Anxiety Disorder - Controlled Comparisons.

At present there is no adequate review of the psychological treatments of anxiety states and generalised anxiety disorder. So studies investigating the efficacy of psychological approaches with this clinical population will be presented in some detail. A summary of the relevant literature is displayed in Table 4.3.

Raskin et al (1973) reported the results of 10 "chronically anxious" ex-inpatients whose treatment comprised 25 minutes of daily hospital-based frontalis muscle EMG biofeedback for a period of 8 weeks. Anxiety was assessed using a 65-item mood checklist filled out by the patient (Raskin et al 1972),and therapists rated patients' "appearance and complaints". Outcome results were given as ; 6 patients improved, 3 moderately improved, and 1 markedly improved. Unfortunately a number of confounding variables exist. Firstly, the 8 week "treatment period" was preceded by an EMG training phase ranging from 2 weeks to 3 months. Secondly, 5 of the 10 patients were on "moderate doses of chlordiapazide hydrochloride (40 - 80 mg per day)" throughout the study. No follow-up data were presented and no control or comparison group was included.

Canter et al (1975) reported the results of a group of 28 in/outpatients suffering from anxiety neurosis, half of whom received frontalis muscle EMG biofeedback, the remainder a modified version of Jacobson's progressive relaxation (Jacobson 1938). The number of treatment sessions ranged from 10 to 25 over

Table 4.3 : Reports comparing psychological treatments of anxiety states and generalised anxiety disorder.

Authors	Diagnosis; Criteria; N	Treatment Conditions	Treatment Duration	Outcome : Evaluation Re: Differential Treatment Effect
Raskin et al 1973	Chronically anxious; N = 10	1 EMG	8 weeks	6 patients unimproved 3 patients moderately improved 1 patient markedly improved
Canter et al 1975	Anxiety neurosis; N = 28	1 EMG 2 Progressive relaxation	10 - 25 sessions	EMG > Progressive relaxation
Townsend et al 1975	Chronic anxiety; N = 30	1 EMG 2 Group psychotherapy	4 weeks	EMG > Group psychotherapy
Lavallee et al 1976	Free floating anxiety; N = 40	1 EMG + Diazepam 2 placebo EMG + diazepam 3 EMG + placebo 4 placebo EMG + placebo	4 weeks	No difference between treatment groups
Mathews and Shaw 1977	General anxiety; N = 10	1 Thought stopping 2 Cognitive desensitization	8 weeks	Thought stopping = Cognitive desensitization
Benson et al 1978	Anxiety neurosis; N = 32	1 Self hypnosis 2 Meditational relaxation	8 weeks	Self hypnosis = Meditational relaxation
Lehrer 1978	Anxiety neurosis; N = 20	1 Progressive relaxation 2 Waiting list	3 weeks	Progressive relaxation > Waiting list
Leboeuf and Lodge 1978	Chronic anxiety; N = 26	1 EMG 2 Progressive relaxation	12 - 14 weeks	EMG = Progressive relaxation
Raskin et al 1980	Anxiety neurosis; DSM III; N = 55	1 EMG 2 Progressive relaxation 3 Transcendental meditation	6 weeks	EMG = Progressive relaxation = Transcendental meditation

(Table 4.3 contd)

Woodward and Jones 1980	General anxiety; N = 27	1 Cognitive restructuring 2 Modified systematic desensitization 3 Cognitive behaviour modification 4 Waiting list	8 weeks	Cognitive behaviour modification > Modified systematic desensitization > Cognitive restructuring = Waiting list
Hutchings et al 1980	General anxiety; N = 70	1 Anxiety management training 2 Applied relaxation training 3 Relaxation only 4 Placebo 5 Waiting list	6 weeks	Anxiety management training > Applied relaxation training = Relaxation only = Placebo > Waiting list
Ramm et al 1981	Free-floating anxiety; N = 12	1 Positive-anxiety management training 2 Negative-anxiety management training	6 weeks	Positive-anxiety management training = Negative-anxiety management training
Jannoun et al 1982	Generalized anxiety; N = 26	1 Anxiety management training after : 2a 4 weeks wait 2b 6 weeks wait 2c 8 weeks wait	6 weeks	Anxiety management training > Waiting
Last et al 1983	Generalized anxiety; N = 1	1 Coping self-statements 2 Paradoxical intention	11 weeks	Coping self statements = Paradoxical intention
Barlow et al 1984	GAD; PD; DSM III; N = 20	1 EMG + cognitive behaviour ther. + progressive relaxation 2 Waiting list	14 weeks	EMG + cognitive behaviour therapy + progressive relaxation > Waiting list

(Table 4.3 contd).

Tarrier and Main 1986	Generalized anxiety; N = 50	1 Applied relaxation training a Participant demonstration b Written instructions c Taped instructions d Participant demonstration + written instructions + taped instructions 2 Waiting list	6 weeks	Applied relaxation training > Waiting list
Durham and Turvey 1987	Generalized anxiety; N = 40	1 Behaviour therapy 2 Cognitive therapy	6 months	Behaviour therapy = Cognitive therapy
Lindsay et al 1987	Generalized anxiety N = 40	1 Cognitive behaviour therapy 2 Anxiety management training 3 Lorazepam 4 Waiting list	4 weeks	Cognitive behaviour therapy > Anxiety management training > Lorazepam > Waiting list
Butler et al 1987a	GAD; RDC; N = 45	1 Anxiety management 2 Waiting list	12 weeks	Anxiety management > Waiting list
Blowers et al 1987	GAD; DSM III; N = 66	1 Anxiety management training 2 Non-directive counselling 3 Waiting list	10 weeks	Anxiety management training = Non directive counselling > Waiting list

a variable time period. Outcome was determined by patients and therapists rating major anxiety symptoms as having "decreased", "increased" or "not changed". EMG was regarded as superior in producing relief from anxiety symptoms. Of the 14 EMG patients, 12 were rated as "improved" and 2 as "no change" by both patient and therapist. Of the 14 progressive relaxation patients 7 rated themselves as "improved" and 7 reported "no change" - the therapist ratings were 6 and 8 respectively. Unfortunately results may have been confounded by 5 of the 28 patients being on unspecified tranquillizers or sedatives on a p.r.n. basis. No follow-up data were presented.

Townsend et al (1975) reported the treatment results of 8 chronic anxiety inpatients who received group psychotherapy in comparison to 10 chronic anxiety inpatients who received frontalis EMG feedback. Group psychotherapy comprised 16 sessions of 60 minutes duration spread over a 4-week period. Thematic Apperception Test (Murray 1943) picture cards were presented to groups of 4 - 5 patients to promote discussion of anxiety provoking aspects of the pictures followed by intermember support and interaction, and possible methods to cope with anxiety. EMG biofeedback consisted of 9 sessions of 20 minutes duration spread over a 4-week period. Assessment measures comprised the State-Trait Anxiety Inventory (STAI) (Speilberger et al 1970), and the Profile of Mood States (POMS) (McNair and Lorr 1964). Overall "patient improvement was arbitrarily defined " resulting in 4 of 10 EMG patients rated as "improved" and none of the group psychotherapy patients achieving

this status. It was concluded that EMG was superior to group psychotherapy. Unfortunately this study has a number of major shortcomings. Firstly, a rather high drop-out rate existed with only 18 patients from an original total of 30 completing the study. Secondly, of the 18, 2 stopped medication, 2 increased medication, 6 had their medication changed, and 8 continued medication unchanged. Thirdly, a range of psychotropics were used throughout the study including chlorpromazine, diazepam, trifluorperazine hydrochloride, and thiordiazpine, all dispensed in varying dosages. Fourthly, patients classified as receiving EMG treatment also "practised deep muscle relaxation for one-half hour each day using tape recorded instructions". Fifthly, only 2 EMG patients were available for 6-month follow-up, and Townsend et al (1975) admitted that only "anecdotal" follow-up impressions could be made.

Lavallee et al (1976)investigated 40 free-floating anxiety outpatients' response to EMG frontalis biofeedback and diazepam in a variety of controlled comparisons. Patients were equally distributed between one of four treatments, including EMG + diazepam, EMG + placebo diazepam, placebo EMG + diazepam, and placebo EMG + placebo diazepam. EMG treatment consisted of 30-minute sessions, twice per week for a period of 4 weeks. Placebo EMG consisted of the same procedure except that no auditory feedback tone was heard by the patient. Diazepam treatment consisted of 5 mgs t.i.d., or placebo diazepam, according to treatment group. Patients were assessed using the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959), the Institute of Personality and

Ability Testing Scale (IPAT) (Cattell and Scheier 1958), and the de Bonic Trait-State Anxiety Scale (de Bonic 1973). Due to inadequate statistical analysis the results are reported in a somewhat confusing and contradictory manner. Following the treatment period there was a statistically significant reduction in anxiety, as assessed by the HAM-A, for all groups apart from the placebo EMG + placebo diazepam group. However scrutiny of the data did not reveal any actual differences between groups following treatment. At 3 and 6-month follow-up the authors concluded that "it was only the feedback (EMG + placebo diazepam) group who maintained a significant anxiety reduction". However further inspection of the data revealed that at follow-up the placebo EMG + placebo diazepam group did equally as well, if not better. Other major flaws include : firstly, the conclusion that "EMG feedback treatment without diazepam had a more prolonged therapeutic effect for chronic anxious patients" has to be tempered by the fact that placebo EMG + placebo diazepam produce similar results. Secondly, the authors noted that "most patients were taking different drugs before the experiment, usually diazepam or chlordiazepoxide. One week before treatment they were asked to stop taking their usual medication and were put on a schedule of diazepam placebo three times per day, constituting a wash-out period". Unsurprisingly "21 patients dropped out at this stage and were replaced by other subjects". Lavallee et al (1976) do not mention reasons for such a high drop-out rate but it is likely that such patients were experiencing benzodiazepine withdrawal symptoms as perhaps were a

number of patients in the actual study. Thirdly, follow-up results may have been confounded by all patients being routinely placed on diazepam p.r.n. after treatment, although differences in consumption levels between groups at follow-up were not significant.

Mathews and Shaw (1977) reported the results of 10 general anxiety psychiatric outpatients, from an original total of 14, treated with 8 weekly sessions of thought-stopping or cognitive desensitisation. In thought-stopping patients were instructed to relax for 5 minutes, and then to begin concentrating on a designated anxiety thought, the presence of which was to be signalled by the patient as soon as a clear image was obtained. At this point the therapist shouted "stop" and instructed the patients to substitute a pre-arranged alternative thought. In cognitive desensitisation the procedure applied was identical until the point at which the patient signalled that a thought was clear. Then they were not instructed to stop it but instead to tolerate it and allow it to remain for as long as it seemed clear. Clinical ratings of severity were made by an assessor (using a 5-point scale). Patients' self-report comprised a weekly mood scale (McNair and Lorr 1964), and a diary of anxious mood (using a 0 - 10 scale) completed every three hours through the day. Mathews and Shaw (1977) reported that "in terms of changes in clinically rated anxiety, all patients except one were rated to have improved in varying degrees, although only two could be judged virtually symptom free on (1 month) follow-up, and the average rated change

was small (0.8 points on the assessors five point anxiety scale), and the patients average self-rating of improvement was just above 'slightly better'. Unfortunately this study provides somewhat scant information and outcome data. Secondly, it is not clear how many patients comprised each treatment group. Thirdly, as regards drug status the paper only notes that patients "were not receiving any treatment other than maintenance medication".

Benson et al (1978) report results of 32 anxiety neurosis outpatients equally allocated to meditational relaxation or self-hypnosis relaxation. Meditational relaxation was learned by patients adhering to a standard list of instructions comprising sitting quietly with eyes closed, muscles relaxed, and ignoring distracting thoughts for periods of 20 minutes , once or twice daily over an 8-week period. Self-hypnosis relaxation was taught by a psychiatrist who repeated individualised instructions in a soothing monotone characteristic of hypnotic induction procedures, for example; relax and imagine you are floating, drifting, or gliding. Patients were directed to practice the techniques for 10 - 15 minutes three times per day for the first 3 days and thereafter twice daily for the 8-week study period. There was no significant difference between the two treatments. Clinical assessment was conducted by means of the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959). Overall 34% of patients were rated as "improved" on the HAM-A, and approximately 63% of patients "felt improved" on self-rating questionnaires. A number of methodological inadequacies exist in this study. Firstly, there

is no mention of the criteria used to determine improvement / unimprovement. Secondly, there is no mention of the possible significance of 37 of the original 69 patients dropping out. Thirdly, there is no follow-up, and fourthly, no mention of drug status.

Lehrer (1978), in a rather complicated design, compared the effects of progressive relaxation in anxiety neurotic patients with progressive relaxation and alpha feedback in nonpatients. Ten anxiety neurotic patients were given four or five sessions of individual, abbreviated Jacobsonian progressive relaxation (Jacobson 1938) over a three-week period (and were told to practise at home for one hour daily), and 10 anxiety neurotic patients served as waiting-list controls. Ten nonpatients were assigned to each of the same conditions and an additional 10 nonpatients were given four sessions of alpha feedback. Regarding the patient groups alone Lehrer (1978) noted that reported anxiety, as measured by the state anxiety scale of the State-Trait Anxiety Inventory (STAI) (Speilberger et al 1970), "decreases significantly more in the relaxation group than in the control group". Lehrer (1978) addressed one of the major limitations of the study by stating that "it is possible that the effect in the present study was also due to drug intake in the patient group, since most of the patients in the sample had histories of taking tranquillizers". Furthermore, no follow-up was conducted.

Leboeuf and Lodge (1980) selected 26 chronic anxiety outpatients and assigned them non-randomly to either frontalis EMG,

or slightly-modified Jacobson's progressive relaxation (Jacobson 1938). Over a 12 - 14 week period both groups received 16 sessions each lasting approximately 30 minutes. Both groups showed statistically significant decreases in anxiety during treatment but there was no difference between groups in magnitude as assessed by the STAI and the Taylor Manifest Anxiety Scale (TMAS) (Taylor 1953). Changes in anxiety symptoms were rated by the referring psychiatrist using the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959), and a 7-point 'clinical improvement scale', pre, post, and at 3 months follow-up. Using these measures only 3 of 13 in the progressive relaxation group, and 2 of 13 in the EMG group achieved moderate improvement, and 6 and 5 respectively achieved slight improvement. These results were maintained at follow-up. No patients demonstrated marked improvement, and Leboeuf and Lodge (1980) conclude that their success rate "was quite typical of the response of anxiety neurotics to placebo drugs". Furthermore they noted that "a decrease on an anxiety questionnaire while valid may not be clinically significant" as "few patients in each group showed more than marginal improvement". In conclusion they noted that EMG biofeedback was unlikely to be a successful treatment for anxiety "since there is an increasing awareness that anxiety neurosis consists of many dimensions of behaviour other than physiological ones and that each aspect of the patients problem may need to be treated using a variety of techniques". While this paper addressed some of the issues neglected in previous studies it has one major drawback in that "most of the patients were on

various tranquillizer medications".

Raskin et al (1980) report the results of 55 anxiety neurosis volunteers of whom 31 completed a 6-week baseline period (during which psychological, social, and physiological data were obtained), followed by a 6-week treatment period, and a 6-week post-treatment period in which data comparable to the baseline data were collected. Patients were followed up at 3 to 18 months. Three treatment groups were compared, namely; (a) EMG frontalis feedback - conducted for 1 hourly sessions, 3 times per week, for 6 weeks; (b) modified progressive relaxation - conducted according to the same schedule; (c) transcendental meditation - involving individual instruction and lectures over 4 consecutive days, followed by "weekly checking by the transcendental meditation trainer", and 20 minutes practice, twice daily, over the six-week study period. Outcome results suggested that "there were no differences between treatments with respect to treatment efficacy". Forty per cent of the subjects were rated as having clinically significant decreases in their anxiety as defined by scores on the Taylor Manifest Anxiety Scale (TMAS) (Taylor 1953), and the Current Mood Checklist (CMCL) (Raskin et al 1972). These improvements were usually maintained at follow-up. However Raskin et al conclude that "relaxation therapies as a sole treatment appear to have a limited place in the treatment of chronic anxiety" In discussing the limitations of the study Raskin et al (1980) noted that their subjects were a self-selected group of highly motivated individuals recruited via public advertisements. Secondly, "subjects taking

prescription medications to relieve anxiety were also included".

Woodward and Jones (1980) selected 27 general anxiety outpatients from a hospital waiting list. Subjects were randomly assigned to one of four groups. a.) Seven patients received "cognitive restructuring" involving the identification of anxiety -producing irrational beliefs, followed by the production of more adaptive self-statements. In addition patients were directed to cognitively rehearse self-instructional ways of handling anxiety and coping in imagination during treatment sessions. b.) Seven patients received "modified systematic desensitization" reported as being identical to that of the cognitive restructuring group, the only difference being that relaxation was the method of coping employed. In addition subjects practiced relaxation at home using taped instructions. c.) Six patients received "cognitive behaviour modification" presented as a combination of "cognitive restructuring" and "modified systematic desensitazation" as outlined by Meichenbaum (1974). In the initial sessions cognitive restructuring was emphasised while in the latter relaxation training was promoted. d.) Seven patients comprised a waiting list no-treatment control group and were assessed at initial interview and two months later. The three active treatments consisted of 8 group sessions (one per week) each lasting approximately 1 hour and 15 minutes. A number of assessment measures were used pre- and post-treatment including the Zung Self Rating Anxiety Scale (Zung 1971), the Fear Survey Schedule (FSS) (Wolpe and Lang 1964), and the Internal and External Control Scale (IE)(Rotter 1966). The

combined treatment "cognitive behaviour modification " proved to be statistically superior to the other two active treatment groups and the waiting list group on the Fear Survey Schedule (FSS) (Wolpe and Lang 1964). Cognitive behaviour modification also resulted in a significant decrease in subjective anxiety measured by patients' diary score in comparison to cognitive restructuring alone. In fact, cognitive restructuring failed to result in any apparent improvement on the dependent variables mentioned. Woodward and Jones (1980) concluded their results demonstrate that " a multidimensional approach to treatment, for example cognitive behaviour modification, is more likely to succeed with this type of patient than treatments comprising one element only, as does cognitive restructuring".

While this is the first paper to propose and evaluate a more pragmatic approach to the managment of generalised anxiety, namely that of cognitive behaviour modification, it is unfortunate that no information regarding patients' drug status was available, and no patients' or referring physicians' assessment of level of clinical improvement was reported. Furthermore a follow-up of more than 1 month would have been useful.

Hutchings et al (1980) screened approximately 800 general psychology students at the University of Kansas, and selected 70 students, scoring in the upper 15% of both the short form of the Taylor Manifest Anxiety Scale (Bendig 1956), and the neuroticism scale of the Eysenck Personality Inventory EPI (Eysenck and Eysenck 1968), as suffering from general anxiety. Subjects were randomly

allocated in equal numbers of 15 per group, to one of 5 experimental conditions as follows :- a) "Anxiety Management Training" (AMT) based on Suinn (1977), introduced with a self-control rationale followed by progressive relaxation. Structured rehearsal involved subjects visualising an anxiety provoking scene from their past and then switching off the anxiety and practising "relaxing away the anxiety". Subjects were instructed to practise relaxation at home twice daily. b) "Applied Relaxation Training"(ART) utilized the same self-control rationale, homework assignments, and application instructions as AMT. However the ART procedure omitted structured rehearsal, and substituted more elaborate and varied relaxation instructions. Six different audiotaped relaxation instructions were prepared for this purpose, each tape introducing a new variation (eg. autogenic exercises, guided imagery). c) "Relaxation Only" (RO) employed the same six audiotaped relaxation instructions and the same homework schedule used in ART. RO differed in that subjects received a "passive rationale" which suggested that relaxation would automatically "supplant anxiety". There was no mention of self-control or instructions concerning the application of relaxation in anxiety-provoking situations. d) "Placebo" received a passive rationale similar to that used in the RO condition which suggested that anxiety would dissipate as they continued in treatment. To this end subjects were shown six 1 hour videos with topics related to psychology (eg. depression, sex roles, aggression). Vaguely distinguishable impressions of people's

faces, blurred movement, fire etc. were superimposed on the film for random intervals of 1 - 15 seconds in order to "unconsciously extinguish " subjects' anxiety. e) "No-treatment" waiting list controls completed pre- and post-test assessments with no intervening treatment.

All "active " treatments (ie a,b,c,d) were conducted in group settings of 5 - 7 subjects who met once per week for a period of 6 weeks, each session lasting 1 hour and 15 minutes. Treatment outcome was assessed by a number of state-trait anxiety questionnaires including the State-Trait Anxiety inventory (STAI) (Speilberger et al 1970), the Anxiety Symptom Checklist adapted from Nicoletti (1972), the short form of the Taylor Manifest Anxiety Scale (TMAS) (Bendig 1956), and the neuroticism Scale from the Eysenck Personality Inventory (EPI) (Eysenck and Eysenck 1968). In summary, on six of the eight measures of state or trait anxiety collected post-treatment, subjects in the AMT exhibited lower levels of anxiety than no-treatment waiting list controls, and on four of these measures subjects in the AMT condition also exhibited less anxiety than RO, and placebo subjects. ART was consistently less effective than AMT. Subjects in the ART condition differed from no-treatment waiting list controls on only four of the eight measures collected at post-treatment and never differed from RO or placebo subjects. Twelve-month follow-up was conducted by postal questionniare with a 60% return rate which provided inadequate data for detailed analysis. This paper has a number of major limitations. Firstly, the possible unrepresentative nature of the

sample population. Secondly, the unusual method of subject recruitment and diagnostic criteria. Thirdly, a lack of any subjects' or referring agents' assessment of degree of clinical improvement or unimprovement. Fourthly, lack of information concerning level of prescribed medication. Fifthly, although Hutchings et al (1980) stated that from the 70 selected subjects, 7 dropped out, post-treatment results are presented for only 58 subjects.

Ramm et al (1981) selected 12 free-floating anxiety outpatients and randomly allocated them in equal numbers to either anxiety management with positive self-instruction (P-AMT), or anxiety management with negative self-instruction (N-AMT). All patients had six sessions, presumably individually, each lasting one hour. Patients attended twice during the first week and weekly thereafter for four weeks. All patients were told that they would be "taught to deal with anxiety by learning appropriate self-instructional methods". Treatment sessions were divided into three main parts - discussion, rehearsal, and homework setting. "Discussion" entailed eliciting patients' coping strategies, checking that treatment instructions were being adhered to, and discussing any difficulties that had arisen between sessions. "Homework setting" entailed selecting anxiety-provoking situations which patients should confront, and ensuring that they kept a diary of how anxious they felt in such situations. Both "discussion" and "homework setting" parts of treatment were similar for both P-AMT and N-AMT patients. "Rehearsal" of the use of self-instructional

cue cards was the main differentiating feature between treatment conditions, the self-instructions on the cue card were "positive" or "negative". Nine statements were on the positive cue card, for example ; 1. I can learn to control my behaviour, 2. I can cope with these feelings, 3. These awful things don't mean anything dreadful will happen to me, 4. These terrible feelings will pass eventually . Nine statements were also on the negative cue card, for example; 1.I'm really going crazy, 2. These feelings are out of my control, 3. I seem to be getting steadily worse, 4. I'm going to make a fool of myself. All patients within each treatment condition used the same cue card. Patients were asked to carry their card with them at all times, and to read it three times, aloud if possible, when they experienced any anxiety! If they did not experience anxiety during a day, they were asked to read it before going to bed at night! During rehearsal, the therapist asked patients to imagine themselves in a difficult situation, and prompted patients with positive or negative self-statements for respective treatment conditions. Patients were assessed pre- and post-treatment and at 3 and 6-month follow-up. Assessment measures comprised the Wakefield Depression Questionnaire (Snaith et al 1971), the Fear Questionnaire (Marks and Mathews 1979), and 5 Likert-style anxiety questions and 4 Likert-style target problems designed by the authors. Ramm et al (1981) concluded that "overall changes in anxiety states with either form of AMT were not impressive. Any slight gains that did exist at the end of treatment were no longer present by one month follow-up.

Unsurprisingly too few patients attended for six-month follow-up to warrant analysis. This study also has serious shortcomings. Firstly, and most importantly, the ethical issue of the entire "negative self-instruction" component of the N-AMT whereby patients are instructed to rehearse such statements as "I'm really going crazy". A treatment approach such as this may potentially worsen a patient's condition. Secondly, a rather small sample size. Thirdly, a lack of any information on concomitant drug treatment.

Jannoun et al (1982) randomly allocated 26 generalised anxiety psychiatric outpatients to one of three groups which differed only in length of time patients waited for treatment. Group 1 waited for 4 weeks, group 2 had a 6-week wait, and group 3 had an 8-week wait. All patients received five treatment sessions over a 6-week period, and one "booster " session 6 weeks after the end of treatment. Treatment was presented to all patients as a self-help programme modified from Suinn and Richardson's Anxiety Management Training (AMT) (Suinn 1977). The main treatment components listed by Jannoun et al (1982) were a) "self monitoring" - patients kept a daily record of anxiety level and drug intake, b) "instruction booklets" - explained the treatment plan, and provided information about the psychophysiology of anxiety, and described the uses and limitations of anxiolytic drugs, c) "muscle relaxation" - learned from audio-taped instructions and practised at home, and d) "cognitive control" - patients were taught to evoke anxiety-provoking images, and engage in positive self-talk. Patients were assessed pre- and post-

treatment, and at follow-up 4 weeks and 10 weeks thereafter. Outcome was assessed using the Hamilton Anxiety Scale (HAM-A)(Hamilton 1959), the Hamilton Depression Scale (HAM-D)(Hamilton 1967), the Leeds Self-Assessment for Anxiety and Depression Scale (LSAA, LSAD) (Snaith et al 1976), and the State-Trait Anxiety Inventory (STAI) (Speilberger et al 1970). All the anxiety and depression measures showed a significant reduction from pre- to post- treatment, and these improvments were maintained at follow-up. There were no significant changes in anxiety during any of the waiting periods prior to treatment. Although this study claimed to report the effectiveness of a brief, time-limited, cost-effective treatment approach it nevertheless has a number of limitations. Firstly, when referred for treatment "22 of the 26 patients were using anxiolytic drugs regularly and 3 of them were also using antidepressants". At the end of treatment, "5 patients were abstaining, 6 showed a decrease in drug intake while 5 remained the same". While reduction in drug dependency is to be commended it is uncertain how this may have influenced the overall results. Secondly, although the study achieved statistically significant results there was no assessment of patient or referring agents' rating of degree of clinical improvement.

Last et al (1983), following from the results of Beck et al (1974), suggested that generalised anxiety patients exhibit "catastrophic cognitions". Last et al (1983) investigated the relative effectiveness of two cognitive strategies namely "coping self-statements" (Meichenbaum 1977), and "paradoxical intention"

(see Ascher 1980; Chambless and Goldstein 1980, for detailed review of this technique) in an individual with generalised anxiety disorder. The patient was treated within a small group of individuals with other anxiety disorders, mostly phobias. Treatment consisted of 11 weekly sessions that were 1 hour to 1 hour and 30 minutes long. During session 3,5,6, and 8 the strategy for "paradoxical intention" was utilized; during sessions 4,7,9, and 11 the strategy of "coping self-statements" was used. A fear questionnaire (Marks and Mathews 1979) was completed at pre- mid- and post-treatment and at 12-month follow-up. In addition each of 5 anxiety-provoking situations were rated both for degree of fear and degree of avoidance using a 9 -point scale (Watson and Marks 1971) pre-, during-, post-treatment, and at follow-up. No statistical technique was used to analyse the data although they were presented graphically and some raw data scores provided. Last et al (1983) noted that their results "do not point clearly to a differential treatment effect for the two cognitive strategies" although the patient reported a preference for the "coping self-statement" strategy. It is also interesting to note that reduction in symptomatology did not actually occur during the two treatment phases, but occurred after treatment had ceased "primarily during the follow-up phase of the study ". Last et al (1983) also stated that their single case study could "in no way provide an adequate test for the efficacy of this treatment approach" (ie. "coping self-statements").

Barlow et al (1984) report the results of eleven patients meeting DSM-III criteria for panic disorder (PD), and nine meeting the criteria for generalized anxiety disorder (GAD). Five GAD and five PD patients were treated, with the remainder assigned to a waiting-list control group. All treated subjects were given progressive relaxation training and frontalis EMG biofeedback combined with cognitive behaviour therapy (CBT) during 18 sessions, over a 14-week period. The relaxation training was adapted from Bernstein and Borkovec (1973), and consisted of tension-relaxation exercises in addition to cue-controlled relaxation associated with the subvocalized word "relax". Subjects received 12 clinic relaxation training sessions, and were required to practise relaxation at home at least once per day. Subjects also received a total of 8 EMG biofeedback sessions. The cognitive -behavioural component of treatment was based on Meichenbaum and Turk's (1973) stress innoculation training, and Beck and Emery's (1979) cognitive therapy for anxiety disorders. The strategies taught included coping self-statements and cognitive restructuring of anxiety-provoking thoughts. Subjects received 12 sessions of CBT. Waiting-list control subjects remained untreated for 14 weeks, and completed the assessment measures at the beginning and end of this period. A wide range of assessment measures were used pre- and post-treatment, and included the State-Trait Anxiety Inventory (STAI) (Speilberger et al 1970), the Beck Depression Inventory (BDI) (Beck et al 1961), the Psychosomatic Symptom Checklist (Cox 1975), and at pre-treatment only the Cognitive Somatic Anxiety

Questionnaire (CSAQ) (Schwartz et al 1978). In addition, all subjects were required to self-monitor their anxiety levels in a daily diary using a 0 - 8 scale. Pre- and post-treatment two clinicians rated each subject independently on a 0 - 8 clinical severity scale. Patients were followed up at least 3 months post-treatment (range 3 months to 1 year). Barlow et al (1984) concluded that their results "indicate a clear effect for psychological treatment of anxiety states (in comparison to no treatment controls) with further improvement noted in most cases at follow-up". Furthermore they noted that "this change was pervasive and broad based" with effects evident on daily self-monitored diary measures, questionnaire measures, and overall clinical ratings of severity. Interestingly there were no significant differences in outcome between GAD and PD. Despite the generally positive pattern of results, changes in clinical ratings of improvement were not correlated at any point with reduction in EMG. In general Barlow et al (1984) presented a relatively well-controlled study incorporating specific treatment approaches designed to alleviate the cognitive and somatic components of GAD. Unfortunately there was no mention of the drug status of patients, and the number of GAD patients was rather small.

Tarrier and Main (1986) randomly allocated fifty consecutive "generalized anxiety" patients, referred to a district psychology department, to one of four Applied Relaxation Training (ART) conditions, or a waiting-list control group.

The four ART treatment groups were each instructed by different methods ; (a) handout (written instructions), (b) tape (taped instructions), (c) participant demonstration (verbal instruction and practice), and (d) combined methods (written and taped instructions to take home, with verbal instruction and practice during treatment sessions). The ART method had the following components : a) self-monitoring of anxiety levels, b) correct breathing, c) progressive muscle relaxation, and d) positive mental imagery. Assessment measures conducted pre-and post-treatment comprised the Symptom Rating Test (SRT) (Kellner and Sheffield 1973), and the Epstein-Fenz Anxiety Scale (EFAS) (Fenz and Epstein 1965). At post-treatment patients rated the benefit of treatment on a three-point scale (0 = none or minimal benefit, 1 = beneficial, 2 = very beneficial). No significant reductions in total SRT and EFAS scores between pre- and post-treatment emerged for the the four individual ART treatment groups and the waiting-list group. Similarly no significant reductions in SRT subscales pre- and post-treatment for individual ART treatment groups emerged. Three of the individual ART treatment groups showed a significant pre- post-treatment reduction on only one subscale of the EFAS, while the remaining ART group showed a significant reduction on two EFAS subscales. Subsequently all four ART results were amalgamated, producing significant pre- post-treatment reductions of the EFAS total and the three subscales as well as on the SRT total and one of three subscales. Tarrier and Main (1986) report that "approximately 70% of the treated groups

reported at least some benefit". However this result should be regarded with some caution as it was "considered that 60% of subjects were in need of further treatment". This study has a number of limitations. Firstly, only 30% of those who received some form of ART were not taking psychotropic medication. Secondly, no actual follow-up data are presented. Thirdly, Tarrier and Main (1986) concluded that "all four methods proved superior to a waiting-list control". However this superiority was only marginal when the four ART conditions are regarded separately and it was only by combining ART treatments that slightly more respectable degrees of significance were achieved.

Durham and Turvey (1987), from an initial sample of 68 generalised anxiety outpatients provisionally accepted for study inclusion, reported outcome data on 40 patients randomly assigned to either behaviour therapy (BT) or cognitive therapy (CT). The two treatment conditions followed a protocol based on Beck and Emery's (1979) unpublished treatment manual. All patients received a maximum of 16 hours individual therapy over a maximum of 6 months. For most patients treatment consisted of 1 hour weekly sessions. There was no difference in the mean amount of therapy given to patients in each of the treatment groups. Durham and Turvey (1987) note that BT and CT had the "same style but differed in content". Assessment measures included a modified Zung Anxiety Status Inventory (ASI) (Zung 1971), the Beck Depression Inventory (BDI) (Beck et al 1961), the Modified Somatic Perception Questionnaire (MSPQ) (Main 1983), the Automatic Thoughts

Questionnaire (ATQ) (Hollon and Kendall 1980), and the modified Dysfunctional Attitude Scale (DAS) (Burns 1980). In addition up to five specific problems and goals were rated on a 9-point scale at initial assessment, discharge, and follow-up, by the patient, the therapist, the patient's spouse or close relative, and an independent assessor. Patients also kept a daily diary recording their maximum severity of anxiety each morning, afternoon, and evening on a 9 - point scale. At discharge and 6-month follow-up patients and the independent assessor made a global assessment of patients' satisfaction with treatment, on a 9 - point scale. Durham and Turvey (1987) concluded that " at the end of treatment there was no difference between CT and BT in the amount of improvement observed". The clinical significance of the effects of treatment suggested that at post-treatment 25% of patients showed slight or no change, 20% were moderately improved, and 54% had markedly or completely improved. However at 6-month follow-up there was a significant trend for the CT patients to maintain or improve upon their post-treatment gains, and for the BT patients to revert back to their mid-therapy scores. By follow-up 62% of CT patients were still rated as markedly or completely improved while only about 30% of BT patients were rated as such. This study provides one of the most thorough reports to date in terms of number and range of assessment measures. Unfortunately it is flawed in that 65% of patients were taking "medication" at the start of the trial, and "patients were encouraged to reduce medication if possible but therapists made no specific attempts to

help achieve this goal". Furthermore although CT and BT are presented as being different in content "the CT condition included behavioural techniques when appropriate". In addition the BT condition while employing behavioural strategies such as relaxation, distraction, and graded exposure also included "the use of positive self-statements and general problem-solving strategies when appropriate". As such the differences between BT and CT may have at times been more apparent than real.

Lindsay et al (1987) reported the results of 40 generalized anxiety outpatients randomly assigned in equal numbers to one of four conditions, a) cognitive - behaviour therapy and relaxation (CBT), b) anxiety management training (AMT), c) lorazepam (BZ), d) waiting-list, - no treatment (WL). The CBT groups received treatment based on that described by Beck and Emery (1979), Beck et al (1979), and Meichenbaum (1974). Treatment focussed on anxiety-related self-statements and underlying assumptions about self, and included challenging automatic thoughts and substituting rational alternatives. Treatment sessions of one hour duration were arranged twice a week over four weeks. Subjects were also given a relaxation tape. The AMT group received treatment based on the work of Suinn and Richardson (1971). The structure of AMT treatment was as similar to the CBT group as possible although the "content and procedures of treatment were extremely different". During treatment subjects were taught relaxation exercises and given a relaxation tape based on Bernstein and Borkovec's (1973) approach. "Anxiety was explained to the patient in terms of

physical symptoms and the emphasis of treatment was always on physical relaxation". The BZ group were prescribed lorazepam 1 mg t.i.d.for 10 days, 1mg b.d.for a further 10 days, and 1 mg nocte for the remaining 10 days, and were seen "for a few minutes only". The WL groups were seem for initial assessment and four weeks thereafter. A three-month follow-up was conducted on the CBT and AMT groups. Assessment measures comprised a) the General Health Questionnaire - 28 items (GHQ) (Goldberg 1978), b) the Zung Self-rating Anxiety Scale (Zung 1971), c) the Modified Automatic Perception Questionniare (MAPQ)(Main 1983), and d) the Cognitive Anxiety Questionnaire (CAQ) - an unpublished scale designed by Lindsay and Hood (1982) to assess automatic thoughts in relation to feelings of anxiety. In addition patients completed a daily diary assessing anxiety level and frequency of anxiety - related cognitions, each rated on 15cm lines. Overall the most immediate and greatest reductions in anxiety occurred in the BZ group. However the initial BZ improvements in clinical status diminished during the course of the trial period and were minimal at the end of therapy. As such no follow-up data were available for the BZ group as over half showed little sustained improvement and were reluctant to discontinue drug treatment for the three months follow-up period in the absence of alternative treatment. Both psychological treatment groups improved as the trial progressed, with the most significant and consistent changes seen in the CBT group. However, at follow-up there was no difference between CBT and AMT groups. While this study has to be commended in attempting

to compare pharmacological and psychological approaches to anxiety management and ensuring that all patients were drug-free for a significant period (6 weeks) prior to study entry, it nevertheless has a few minor limitations. Unfortunately there was no attempt to balance between groups for the degree of therapist-patient contact. It could be argued that the improvements in AMT and CBT groups, in comparison to BZ and WL, were solely due to the amount of psychologist attention patients received as opposed to the specific techniques of CBT and AMT themselves. Indeed this criticism applies to a number of studies previously reviewed in this chapter and requires consideration in future studies comparing pharmacological and psychological interventions. Secondly, Lindsay et al (1987) quoted the Committee on the Review of Medicines' (1980) Report that "benzodiazepine therapy .... be withdrawn gradually .... and that prescriptions be limited to short term use". However, their use of lorazepam 1mg t.i.d. for 10 days prior to graded withdrawal may be regarded as a rather short period of therapy considering the recent more restrictive 1988 guidelines for benzodiazepine prescription recommending treatment periods of 2 to 4 weeks only (Committee on Safety of Medicines 1988). Thirdly, although Lindsay et al (1987) rightly implemented a graded withdrawal programme, it would have been advantageous if this had been a "placebo substitution" withdrawal programme. Use of the latter would have determined whether the increase in anxiety symptoms during graded reduction of medication was due to reduction of BZ per se, or simply a result of reduced tablet intake.

Fourthly, it has been noted that withdrawal symptoms from short-acting benzodiazepines such as lorazepam are more pronounced than those from long-acting benzodiazepines (Rickels et al 1986). Therefore it would have been more efficacious to use a benzodiazepine such as diazepam which is long-acting, and which is regarded as the standard comparative benzodiazepine of choice in clinical trials (Rickels 1978).

Butler et al (1987a) reported on 45 patients (from a total of 63; 18 of whom failed to attend or preferred other treatment) with generalised anxiety disorder (GAD) as defined by Spitzer et al's (1978) Research Diagnostic Criteria. Twenty-two patients were randomly allocated to an Anxiety Management (AM) treatment condition, the remaining twenty-three to a Waiting-List (WL) control group. AM treatment was described to patients in a booklet and presented as a form of self-help. The patient booklet provided information on the nature of anxiety, its common manifestation and precipitants. Methods of eliminating anxiety, for example relaxation, distraction, and identifying and challenging irrational thoughts were also presented in the booklet. Patients were encouraged to reduce avoidance using graded exposure. Taped instructions for progressive muscular relaxation, which was to be practised at home, were provided. Individual treatment sessions, up to one hour in length ranged from 4 - 12. "Booster sessions" were given 2 and 6 weeks after the end of treatment. A post-treatment assessment was carried out 3 months after the start of treatment, and follow-up assessments were conducted 3 and 6 months

later. Assessment measures included the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959), the Hamilton Depression Scale (HAM-D) (Hamilton 1967), the State-Trait Anxiety Inventory (STAI) (Speilberger et al 1970), the Leeds Scales (Snaith et al 1976), the Present State Examination (PSE) (Wing et al 1974), and the General Health Questionnaire (GHQ) (Goldberg and Hillier 1979). Expectations about outcome, suitability of treatment, and anxiety level were rated by patients on a 0 - 8 scale. In summary Butler et al (1987) reported that highly-significant reductions in anxiety and depression occurred in the AM group. In addition these changes were replicated when the WL group also eventually received AM treatment after the comparative study period. Treatment gains were maintained by both groups at 6-month follow-up. Butler et al (1987a) concluded that AM was suitable for treating GAD in primary care as it was "readily understood by patients" and "as well as including procedures for controlling symptoms it deals with anxious cognitions and avoidance behaviour, both of which appear to contribute to the maintenance of anxiety disorders". In their study Butler et al (1987a) have applied a pragmatic, multidimensional, and mixed treatment approach to GAD. This reflects the need to develop therapeutic techniques which address the three main components, namely somatic, cognitive, and behavioural aspects. Unfortunately a major limitation of this study is that at initial assessment 46% of the patients were taking regular medication. Of the prescriptions 73% were for anxiolytics, 14% for hypnotics, and the remainder for antidepressants and

combined preparations. Secondly, of the 36 patients included at 6-month follow-up, "3 were given anxiolytic medication to help with particular stressors .... and another 9 had received more extensive treatment for anxiety, including taking regular medication.... 7 of these had also received antidepressant medication". So follow-up results may have been confounded by the subsequent pharmacological treatment effects. Thirdly, although Butler et al (1987a) described the patient group as suffering from GAD, it also appears that "patients meeting the criteria for panic disorder as well as GAD were included provided the GAD was the primary disorder". However it was also noted that "using the PSE definition of panic attacks, 13 patients fulfilled the criteria for panic disorder". Given these statements there appears to be a degree of ambiguity concerning the diagnostic features of the patient population.

Blowers et al (1987) out of an original 95 GAD outpatients (diagnosed according to DSM III criteria) presented results on 66 patients randomly allocated to anxiety management training (AMT), non-directive counselling (NDC), or a waiting-list control (WL). Twenty patients received AMT and were given a booklet entitled "Coping with Anxiety", which provided a treatment rationale that "anxiety could be controlled using relaxation and the modification of upsetting thoughts". Patients were taught a brief form of relaxation based on that described by Bernstein and Borkovec (1973). Cue-controlled relaxation was emphasised and regular homework practice was encouraged. The cognitive component of

treatment was an abbreviated form of that described by Beck and Emery (1985). During treatment, time was devoted to identification of patients' anxiety provoking thoughts, and methods of challenging the validity of these cognitions. Blowers et al (1987) also noted that "therapists searched for homework tasks that would throw light on the validity of the thought content being discussed" but for some unexplained reason "avoided giving instructions that might be interpreted as encouraging systematic and regular exposure to anxiety provoking situations". Twenty-two patients received NDC and were given a booklet entitled "Understanding Anxiety" which offered a rationale to the effect that patients could be helped by "becoming aware of and understanding their own thoughts and feelings". Therapists offered a non-directive approach based on that described by Rogers (1957). No relaxation instructions were given, nor was any direct advice concerning anxiety management . Instead, therapists used reflection as their primary technique. Twenty-four WL patients were assessed at time of acceptance into the trial, and again 10 weeks later. AMT and NDC were given 8 sessions of individual treatment each lasting approximately 45 minutes, over a 10-week period. Assessments were conducted pre- and post-treatment and at 6-month follow-up. Assessment measures included the Clinical Anxiety Scale (Snaith et al 1982), the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983), the Speilberger Trait Anxiety Scale (Speilberger et al 1970), and the St. Georges Anxiety Questionnaire (for which no reference was provided). In summary, AMT was significantly more effective than

the WL condition, but there were surprisingly few significant differences in outcome between AMT and NDC either at post-treatment or at 6-month follow-up. Blowers et al (1987) concluded that AMT was effective "but that its superiority to a less structured and less directive alternative remains to be proven". With reference to the modest clinical change reported in the AMT group, Blowers et al (1987) noted that "real life exposure practise was deliberately eliminated so that the effects of brief training in relaxation and cognitive coping could be evaluated in isolation". However Mathews (1984) has argued that anxiety arousal may be a crucial feature in successful treatment, perhaps because it exposes patients to relevant anxiety-evoking stimuli, whether internal or external in nature. Blowers et al (1987) admit that in the absence of exposure, "relaxation and cognitive methods may be only slightly more potent than are relatively non-directive and non-structured methods of psychological counselling". They therefore suggested that their results "can be used to argue for treatment involving a combination of exposure to anxiety-arousing situations and simultaneous practice in cognitive coping methods". In other words, they suggested that treatment should address cognitive, behavioural, and somatic manifestations of anxiety as opposed to the purely cognitive and somatic approach adopted in the AMT programme. Unfortunately, Blowers et al's (1987) results are compromised by the fact that an unspecified number of patients were taking "tranquillizers", and that approximately 30% of the original sample dropped out. No further information being presented on

either of these factors.

4.3 Summary

The efficacy of pharmacological and psychological techniques in the management of GAD is presently inconclusive. Poor methodological design has contributed to the apparent indeterminate nature of outcome results. Ost (1982) attributes lack of efficacy of psychological techniques to the oversimplified passive manner in which anxiety reduction has been managed. For example, the emphasis in the majority of studies to date on techniques such as EMG feedback and progressive relaxation training, without enabling patients to actively develop alternative cognitive and behavioural coping strategies for the management of generalised anxiety in everyday situations. As a consequence multidimensional and mixed treatment approaches have been advocated (Mathews 1985) and more recently adopted. Unfortunately with the exception of Lindsay et al's (1987) study, the efficacy of multidimensional treatments of generalised anxiety has yet to be adequately compared with widely used pharmacological alternatives.

The majority of studies investigating the efficacy of psychological treatments have included patients who were already taking benzodiazepines. This practice is also methodologically unsound. The effect that benzodiazepines may have on the efficacy of behaviour therapy for phobic anxiety has been reviewed by Sartory (1983). Sartory (1983) concluded that the concurrent

administration of benzodiazepines has little effect on the outcome of behaviour therapy although it is possible that, at follow-up, gains made whilst under the influence of the drug are less stable than those made during a non-drug state. This relates to research on state dependent learning where behaviour established under one drug state may not transfer so readily to another drug state (Overton 1966). In addition, other mechanisms, such as who or what the therapeutic success is attributed to has important ramifications. Sartory (1983) suggested that if patients "learn to tolerate fear inducing situations because they trust in the anxiolytic effect of a drug rather than their own clinical improvement, discontinuation of the medication may lead to relapse". Sartory (1983) recommended that "the use of benzodiazepines in behavioural treatment is at best redundant and at worst detrimental" and should therefore be discouraged.

Miller (1986) has highlighted that concurrent taking of benzodiazepines during psychological treatment can misleadingly distort the nature of the patients presenting problem. For example, benzodiazepines may reduce the severity of anxiety symptoms thereby enhancing the apparent efficacy of psychological treatment. Alternatively, irregular medication consumption, especially of short-acting benzodiazepines, when patients fail to take medication as prescribed, may lead to temporary oversedation, followed by episodic withdrawal symptoms with heightened anxiety.

Unfortunately these issues have not been addressed in studies which assume that concomitant benzodiazepine treatment is

equivalent to psychological treatment alone.

From this review the specific area requiring further research is evident. In particular a controlled comparison of the efficacy of pharmacological and psychological treatment, each alone and in combination, in the treatment of GAD.

CHAPTER 5 : AIMS OF PRESENT RESEARCH

The present research consists of a sequence of studies each conducted to meet a series of experimental aims which were derived from the literature reviewed in Chapters 2,3, and 4.

The Pilot Study is divided into two partially-overlapping sections (Ia, Ib); followed by the Main Study (II); a Secondary Study (III); and a Subsidiary Study (IV).

Ia) PILOT STUDY

A controlled comparison of withdrawal symptoms and anxiety recurrence following six weeks double-blind diazepam or placebo treatment, for GAD in primary care.

Ib) PILOT STUDY

A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo in the management of GAD in primary care.

II) MAIN STUDY

A controlled comparison of the efficacy of diazepam, placebo, cognitive-behaviour therapy, diazepam plus cognitive-behaviour therapy, and placebo plus cognitive-behaviour therapy in the management of GAD in primary care.

III) SECONDARY STUDY

A controlled comparison of the characteristics of long-term benzodiazepine users in primary care.

IV) SUBSIDIARY STUDY

Psychological ill-health and attitude to benzodiazepine use and withdrawal among long-term benzodiazepine users.

CHAPTER 6 : PILOT STUDY Ia and Ib.

6.1 Ia) Pilot Study

A Controlled Comparison of Withdrawal Symptoms and Anxiety Recurrence Following Six Weeks Double-Blind Diazepam or Placebo Treatment for Generalised Anxiety Disorder in Primary Care.

As previously mentioned in the introductory chapters benzodiazepines are generally accepted to be the treatment of choice in anxiety states, and superior to placebo (Greenblatt and Shader 1974). However many studies may be criticised on methodological grounds (Solomon and Hart 1978). Furthermore a number of studies have even suggested that placebo may be as effective as anxiolytic medication, especially for patients with low to moderate levels of anxiety (Johnstone et al 1980; Shapiro et al 1983). The existence of benzodiazepine dependence is now incontrovertible (Petursson and Lader 1981; Marks 1983a; Tyrer et al 1983), although estimates of the numbers of users who are affected by withdrawal symptoms vary widely (Hallstrom and Lader 1982). Apart from a singular notable exception (Murphy et al 1984), controlled studies of benzodiazepine withdrawal after the administration of short-term therapeutic doses are lacking. In addition, despite approximately 85% of all benzodiazepines being prescribed by GPs (Rose 1983), and most anxiety disorders being treated in primary care, with less than 10% being referred to psychiatrists (Shepherd et al 1966), the efficacy of anxiolytics

has hitherto largely been based on studies with highly skewed psychiatric outpatient groups (Greenblatt and Shader 1974). The lack of adequately controlled studies investigating the efficacy and subsequent withdrawal of short-term benzodiazepine treatment, at the recommended dosage for GAD, in a primary care setting, with patients who had not recently used or been dependent on minor tranquillizers, prompted the first of this series of studies.

This section of the pilot study aims to compare the effectiveness of diazepam versus placebo in the management of GAD over a six-week double-blind period in a primary care setting. The effect of placebo on anxiety level was assessed during one week single-blind treatment with placebo before double-blind treatment was started. Withdrawal reactions from diazepam were investigated during a two-week withdrawal period, when single-blind placebo was substituted for the double-blind active treatment.

6.1.1 Subjects

Patients presenting to general practitioners (GPs) with a GAD, who were thought suitable for pharmacological or psychological treatment were referred for study inclusion. Following GP assessment of morbidity the present author then assessed patient characteristics, present mental state, and severity of illness. Patients were considered suitable for study inclusion if they met the following criteria during detailed assessment :-

a primary diagnosis of GAD according to Present State Examination (PSE)(Wing et al 1973), DSM III (1980), and Research Diagnostic

Criteria (Spitzer et al 1978); a minimum score of 15 on the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton 1959); symptoms that had lasted for at least one month; no continuous and prolonged use of benzodiazepines in the past 12 months; not taken psychotropic drugs at time of initial assessment or in the previous three weeks; aged 18 to 65 years of either sex; and having given written consent.

Patients were excluded if they met any of the following criteria :- known to have a history of hypersensitivity reaction to, or abuse of, or dependence upon benzodiazepines; exhibiting any evidence of epilepsy, organic brain disease, or other neurological deficits; exhibiting any significant cardiovascular, hepatic, renal, respiratory, or endocrinological disease; considered to have a high risk of suicide; evidence of alcohol abuse; if female, patients pregnant or lactating; if female, patients not using contraceptive though required; previously included in the present study; patients attending other therapists, either professional or lay therapists. Patients with primary phobic or depressive disorders were specifically excluded, although patients with minor secondary phobic or depressive features were eligible for study inclusion.

A total of thirty-seven patients were referred by GPs for study inclusion. Three patients were not included as their anxiety state was not of adequate severity to meet entry criteria. One patient was not admitted to the study due to inability to meet diagnostic criteria; a primary depressive disorder was present.

One patient was withdrawn from the study following the use of non-prescribed benzodiazepines, and one patient dropped out prior to commencement of active therapy. Thirty-one patients were included in the pilot study.

6.1.2 Treatments

The thirty-one patients received one of three treatments : diazepam (n=10), placebo (n=11), or cognitive-behaviour therapy (CBT) (n=10). The main demographic details of patients included in the pilot study are shown in Table 6.1. Information concerning patients' previous benzodiazepine prescription, and previous episodes of anxiety were supplied by GPs from practice records. The results of the diazepam and placebo groups alone will be presented in this section as these groups underwent a more detailed assessment with regard to treatment process measures and withdrawal symptoms. (A comparison of the relative efficacy of treatment outcome and follow-up for diazepam vs. placebo vs. CBT will be presented separately in a following section of the pilot study results - PILOT STUDY Ib).

All patients underwent a one-week single-blind placebo wash-in period, during which patients were unaware of their drug status. Then diazepam and placebo treatment groups received either 5mg diazepam three times daily or placebo three times daily double-blind for a six-week period. Following this period, both groups received a further two weeks single-blind placebo period, during which patients were unaware of their drug status, in order to

assess pharmacological withdrawal symptoms after cessation of benzodiazepine treatment. All drugs were dispensed in identical capsules packaged in dosettes, which were returned to the present author at each assessment to check compliance. Only enough medication to last to the next scheduled appointment was dispensed at any one time.

6.1.3 Procedure

Following initial GP and the present author's baseline assessments, which together lasted approximately one hour and forty-five minutes, patients were randomly allocated to treatment groups.

Over the six-week double-blind drug period the diazepam and placebo patients were seen individually on four occasions by the present author, and twice by their respective GPs. To compare the impact of diazepam and placebo on cognitive and psychomotor functions (to be reported separately) all patients completed a battery of computerised cognitive and psychomotor tests, as well as drug compliance assessments and adverse symptom checklists during each appointment with the present author.

For diazepam and placebo patients the present author also inquired about response to treatment in a non-directive manner so as to avoid making suggestions of a therapeutic nature. Each patient received approximately three hours and twenty minutes contact with the present author, and thirty minutes GP assessment contact.

Table 6.1 . Demographic Features of Pilot Study GAD Patients.

	CBT (n = 10)	Diazepam (n = 10)	Placebo (n = 11)
Mean age (yrs)	33.5	31.8	36.9
Sex	1M, 9F	2M, 8F	1M, 10F
Duration of symptoms (months)	3.2	4.9	3.2
Nos with history of anxiety	8	6	10
Nos previously prescribed benzodiazepines	7	7	7

6.1.4 Measures

Three primary measures of treatment process and outcome were used in this section of the pilot study.

a.) The Hamilton (1959) Rating Scale for Anxiety (HAM-A) (Appendix 1) was used by the present author as the main treatment process and outcome measure to determine patients' anxiety symptoms.

The HAM-A was designed to assess the severity of symptoms in patients suffering from anxiety neurosis. The HAM-A consists of 14 items, each rated on a five-point (0 - 4) scale. Under each item a number of symptoms and signs are listed, which indicate the range of phenomena to be considered when scoring. The 14 items include anxious mood, tension, fears, insomnia, difficulties in concentration and memory, depressed mood, general somatic symptoms (muscular), general somatic symptoms (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genito-urinary symptoms, autonomic symptoms, and behaviour at interview. The items can be totalled to produce a general factor of anxiety, or divided to produce a bipolar factor contrasting 'psychic' with 'somatic' symptoms. Hamilton (1959) reported reliability correlations as varying between +0.83 to 0.95. The evaluation of presence and intensity of the various items is based on an interviewer's assessment of the patient's condition at the time of interview. Few of the 14 items are clinical signs to be directly observed during interview. The majority of items are symptoms (i.e. patient complaints), and therefore the assessment is based

on the patient's condition during the previous days as recommended by Hamilton (1986). Throughout the present series of studies HAM-A assessments covered the 7 - day period prior to interview. A more detailed and structured scoring system based on specific assessment of the frequency, severity and duration of symptoms, was introduced at initial entry assessment and used consistently thereafter (Hamilton Anxiety Glossary - Power et al 1985; Appendix 2). The Hamilton Anxiety Glossary (HAM-G) (Power et al 1985) was developed to improve inter-rater reliability of the HAM-A and is similar in structure and intention to the glossary developed by Williams (1984) for the Hamilton (1960) rating scale for depression (HAM-D).

The HAM-G was evaluated by 16 clinical pychologists during anxiety assessment training using pre-recorded videotaped interviews with GAD patients. Prior to HAM-G training the standard deviation of the 16 psychologists' HAM-A scores was 4.61. When rating the same interview using the HAM-G, the standard deviation was 1.86, thereby illustrating a statistically significant improvement in reliability ($t = 3.427$, $df = 14$, $p < 0.05$) (Snedecor and Cochran 1967). In the above training session the HAM-G also significantly reduced the HAM-A scores from a mean of 32 (range 25 - 39) prior to use, to a mean of 22.37 (range 19 - 25) when adhered to ($t = 7.06$, $df = 15$, $p < 0.01$). It therefore appears that the HAM-G enhances reliability and produces a more conservative HAM-A score.

With the exception of the initial GP assessment (day -7),

undertaken before the placebo wash-in period began, the HAM-A was completed at each assessment interview by the present author, that is, at the end of the placebo wash-in period but immediately before the active treatment period (day 0), and on days 7, 14, 28, and 42 of the six-week double-blind active treatment period. A final assessment was conducted at the end of the two-week withdrawal period (day 56).

b). The Kellner and Sheffield (1973) Symptom Rating Test (SRT) (Appendix 3), designed to measure changes in symptoms of distress in neurotic patients participating in therapeutics such as drug trials, was the main self-report treatment process and outcome measure used.

The SRT consists of a check-list of 38 symptoms; 15 are somatic, and 23 psychological, and the patient rates each symptom on a four-point scale. Kellner and Sheffield (1973) report test-retest reliability correlations as varying between +0.92 to 0.94. Split-half reliability of changes on the SRT score in neurotic outpatients after one month was .+0.89. In a number of validation studies the SRT discriminated significantly between patients and normals. In drug trials the SRT was found to be effective in discriminating between responses to psychotropic drugs and to placebo. Kellner and Sheffield (1973) report the SRT to be a valid and reliable measure of distress. The SRT was completed by the patient at the GP's initial assessment before the placebo wash-in period began. Thereafter the SRT was administered by the current author and completed by the patient to the same schedule

as the HAM-A.

c) Adverse reactions to the drug regimen were recorded by the present author at each assessment interview by means of an open ended interview and check-list of adverse symptoms (Appendix 4).

6.1.5 Results

One-way analysis of variance produced no significant difference on subjects' demographic variables i.e. age and duration of symptoms. No significant difference in mean scores was seen between diazepam and placebo groups on initial HAM-A (day 0) ($t = 1.23$, $df = 19$), and initial SRT (day -7) ($t = 0.062$, $df = 19$). Mean ratings and standard deviations for diazepam and placebo groups on the HAM-A during active double-blind treatment (days 7, 14, 28 and 42), and at the end of the single-blind withdrawal period (day 56) are presented in Table 6.2 and illustrated in Figure 1.

Mean ratings and standard deviations for both groups on the SRT, at day -7 and on the same schedule as the HAM-A ratings are presented in Table 6.3 and illustrated in Figure 2.

Effects of treatment were investigated by computing repeated measures analysis of variance (MANOVA) with treatment group as the between subjects factor and time of assessment as the within subjects factor.

a). HAM-A ratings : The between-group analysis revealed a significant time ($F(5,95) = 12.76$ $p < 0.001$) and interaction effect ($F(5,95) = 3.09$ $p < 0.05$) with no significant group effect.

Table 6.2. HAM-A means and standard deviations (SD) for Diazepam and Placebo groups at each assessment stage during treatment.

	Diazepam		Placebo	
HAM-A	$\bar{X}$	(SD)	$\bar{X}$	(SD)
Day 0	18.9	(3.7)	16.7	(1.1)
Day 7	12.1	(6.6)	13.5	(4.8)
Day 14	10.1	(6.7)	12.8	(5.6)
Day 28	11.0	(7.3)	12.7	(6.3)
Day 42	9.9	(6.3)	12.6	(6.3)
Day 56	14.8	(6.1)	12.1	(6.6)

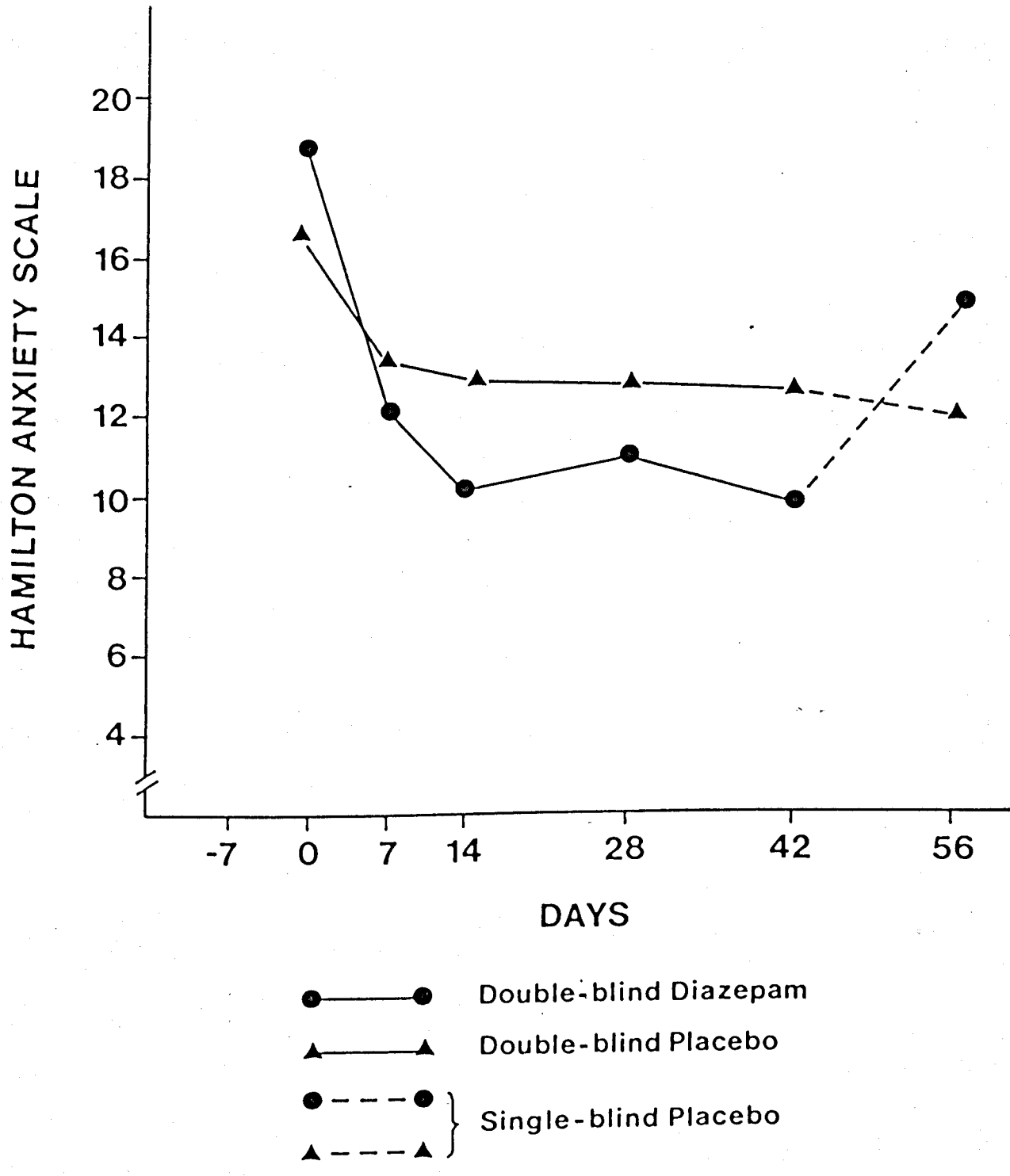

FIG 1 - Effects of Diazepam and Placebo on Hamilton Anxiety Ratings

Table 6.3. SRT means and standard deviations (SD) for Diazepam and Placebo groups at each assessment stage during treatment.

	Diazepam		Placebo	
SRT	$\bar{X}$	(SD)	$\bar{X}$	(SD)
Day -7	38.5	(13.0)	35.0	(12.6)
Day 0	37.1	(20.0)	34.7	(9.7)
Day 7	28.2	(13.9)	27.3	(12.8)
Day 14	24.3	(18.1)	27.2	(13.1)
Day 28	30.4	(18.0)	28.3	(16.0)
Day 42	26.1	(17.3)	27.1	(16.6)
Day 56	38.0	(21.4)	25.8	(17.4)

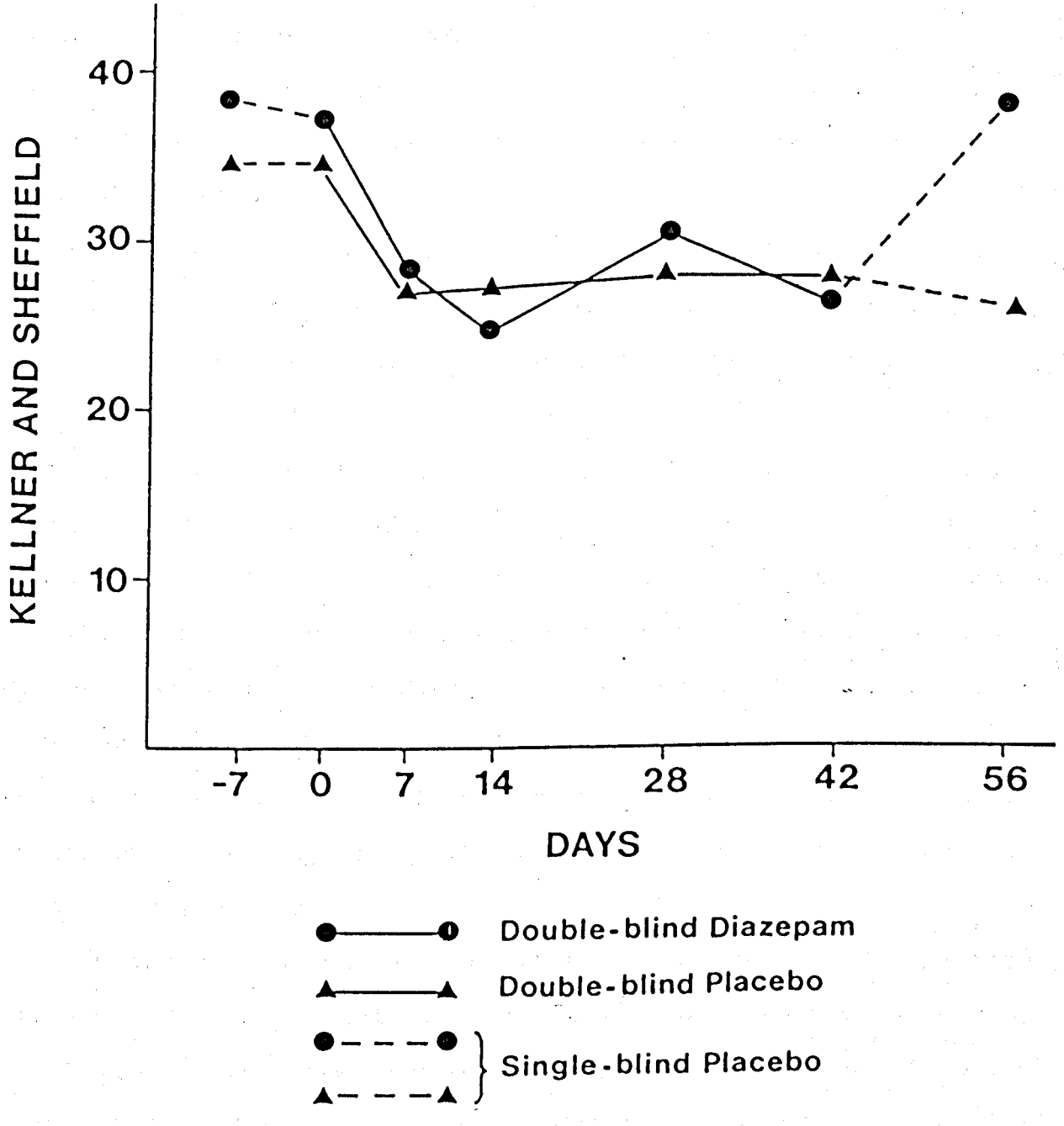

FIG 2 - Effects of Diazepam and Placebo on Kellner and Sheffield Ratings

To assess the simple effects of time within each group a repeated measures within-group MANOVA was performed, which revealed significant changes over the six assessment sessions in both the placebo ($F(5,95) = 3.11$, $p < 0.05$), and diazepam ($F(5,95) = 12.30$, $p < 0.005$) groups.

Within-group treatment response revealed that there was a significant reduction in HAM-A scores for the diazepam patients, during the first week (day 0 - day 7) of active double-blind treatment, ($t = 3.11$, $df = 9$, $p < 0.05$). This was maintained at the end of active treatment, comparing day 0 to day 42, ($t = 5.76$, $df = 9$, $p < 0.0005$). However following single-blind placebo substitution withdrawal (day 56) there was a significant increase in HAM-A scores in comparison to the end of active double-blind treatment (day 42) ($t = 3.01$, $df = 9$, $p < 0.05$). Despite such increases in HAM-A following withdrawal, the diazepam group as a whole were still assessed to be less anxious at day 56 in comparison to the beginning of double-blind active treatment (day 0) ($t = 2.50$, $df = 9$, $p < 0.05$).

Similarly within-group treatment response for the placebo patients revealed a significant reduction in HAM-A scores, during the first week of active double-blind treatment, from day 0 to day 7, ($t = 2.48$, $df = 10$, $p < 0.05$) which was maintained at the end of active treatment, comparing day 0 to day 42, ($t = 2.30$, $df = 10$, $p < 0.05$). However, unlike the diazepam group, the placebo group did not exhibit a significant increase in HAM-A scores following single-blind placebo substitution withdrawal (day 56) when compared

to the end of double-blind treatment (day 42) ($t = 1.46$, $df = 10$). At the end of the single-blind withdrawal period (day 56) the placebo group were also assessed on the HAM-A to be less anxious than at the beginning of double-blind active treatment (day 0) ($t = 2.44$, $df = 10$, $p < 0.05$). There was no significant difference between the treatment groups on any of the individual assessment days.

b) SRT ratings : The SRT ratings revealed a significant time effect ($F(6,114) = 3.48$, $p < 0.005$), and no significant group or interaction effect . To assess the simple effects of time within each treatment group a repeated measures within-group MANOVA was performed, showing that only the diazepam group changed significantly during treatment over the seven assessment sessions ($F(6,114 = 3.08$, $p < 0.001$).

Within-group treatment response comparing initial SRT scores before entry to the study (day -7) and following single-blind placebo wash-in treatment (day 0) failed to show any significant reduction for either the diazepam ($t = 0.33$, $df = 9$), or placebo ($t = 0.18$, $df = 10$) groups. Although a number of within-group trends existed there were no significant changes in SRT scores between individual assessment days for both treatment groups. In particular there was no significant reduction in SRT scores at the end of the active double-blind treatment period (day 42), in comparison to the beginning of double-blind active treatment (day 0) for either group. The increase in SRT scores for the diazepam group following single-blind placebo substitution

withdrawal (day 56) in comparison to the end of active double-blind treatment (day 42) failed to achieve statistical significance. There was no significant difference between the treatment groups on any of the individual assessment days on the SRT.

6.1.5.3 Withdrawal

Adverse withdrawal reactions at the end of the two-week placebo withdrawal period (day 56) were considered to have occurred if (i) there was a quantitative increase in the severity of symptoms from that reported at the end of the double-blind period (day 42), or (ii) new symptoms had emerged that had not previously been reported. Table 6.4 shows increases in previously-occurring symptoms, and the appearance of new symptoms. No patient may have a score in both columns for any one symptom. The diazepam group reported a significantly greater number of both types of withdrawal symptoms for each patient ($t = 8.91$, $df = 19$, $p < 0.005$; $t = 3.69$, $df = 19$, $p < 0.05$) than the placebo group.

6.1.6 Discussion

A significant reduction in anxiety ratings as assessed by HAM-A scores was found in patients who had taken diazepam, and to a lesser extent also in those who had taken placebo. Both drugs were most effective during the first week of double-blind treatment, a result similar to that found by Shapiro et al (1983). The efficacy of both drugs as assessed by the SRT, was less noticeable and few significant results emerged, although the trend

Table 6.4. Adverse withdrawal reactions and number of patients experiencing them.

Treatment Group	Symptoms	Previously Occurring	New Symptoms	TOTAL
Diazepam	anxiety	8	0	8
(N = 10)	restlessness	3	4	7
	difficulty getting to sleep	4	2	6
	disturbed sleep	6	0	6
	apprehension	2	3	5
	dizziness	1	4	5
	nausea	1	3	4
	headaches	0	3	3
	lack of energy	1	1	2
	tremor	0	2	2
	excessive perspiration	2	0	2
	abdominal cramps	0	2	2
	faintness	0	1	1
	chest pains	1	0	1
	loss of appetite	1	0	1
	derealisation	0	1	1
		30	26	56
Placebo	anxiety	1	0	1
(N = 11)	constipation	0	1	1
		1	1	2

was similar in direction to HAM-A scores. This discrepancy between self-ratings and observer-ratings is in accord with Lader's (1985) suggestion that self-report data provide a more conservative assessment of drug efficacy in comparison to trained observer ratings. In addition large standard deviation scores on SRT ratings by both groups (Table 6.3) illustrate the wide range of patients' self-reported anxiety symptoms throughout the study period.

No significant reduction in SRT scores was seen in either group during the initial placebo wash-in period. The reduction in anxiety ratings during the first week of double-blind treatment may have been partly due to factors other than double-blind medication - for example, the introduction of the clinical psychologist assessor, whose sole concern was assessment of efficacy, and who purposely did not provide any direct psychological treatment but, nevertheless, provided increased contact with the patients. This suggests that factors such as amount of contact with patients during drug trials may play a substantial role in determining the outcome of treatment.

A number of problems exist in defining withdrawal symptoms after the end of anxiolytic treatment. A small number of withdrawal scales exist but are either unvalidated (Lader, personal communication 1985), or validated on subjects during withdrawal from long-term, high-dose benzodiazepine abuse (Sellers et al 1987, unpublished report). Owen and Tyrer (1983) suggested that the first symptoms experienced during withdrawal are similar to those of anxiety. Whether these symptoms are a recurrence of clinical

anxiety, or a drug withdrawal reaction is difficult to determine. The emergence of new symptoms during withdrawal however, is less likely to be due to anxiety recurrence. Owen and Tyrer (1983) therefore suggested that the presentation of new symptoms, and a temporary increase in pre-existing symptoms may indicate a withdrawal syndrome.

The results of the present pilot study suggest that withdrawal from diazepam after a short period of treatment by substitution with single-blind placebo leads to an increase in both anxiety and withdrawal symptoms. Graded withdrawal may reduce the number and severity of symptoms, and this will be assessed in the main study to follow (Chapter 7). Nevertheless the results of single-blind placebo withdrawal treatment indicated that the symptoms reported were not reactions that occurred due to the cessation of tablet consumption but were specifically due to the termination of diazepam treatment.

However, not all patients receiving benzodiazepines experience withdrawal symptoms and / or increases in anxiety during withdrawal (Laughren et al 1982). Tyrer (1984b) suggests that over 50% of long-term users can abruptly stop benzodiazepines without any problems occurring. Similarly in the present pilot study only half of the diazepam group exhibited significant increases (defined as increases of $\geq$ 100% of day 42 HAM-A score at day 56) in anxiety during withdrawal. The finding that withdrawal symptoms can occur, after a relatively short period of treatment in a significant percentage of patients, has important implications for management.

The current trend advocates a reduction in the duration of treatment. However the above study suggests that the use of diazepam at normal therapeutic doses, and for what has hitherto been regarded as a safe length of treatment, may result in withdrawal symptoms. During withdrawal many patients are likely to interpret any minor physical or psychological change either as evidence of anxiety recurrence,or evidence of withdrawal problems, thereby magnifying their self-perceived dependency. Furthermore, the expectancy of severe withdrawal reactions that has been highlighted by some sections of the popular press may inadvertently focus patients' attention, and thereby enhance withdrawal effects in patients with suggestible personalities. It is important that such misconceptions are allayed prior to the commencement of withdrawal.

The results of this section of the Pilot Study were published by Power et al (1985).

Although the sample size of this section of the pilot study is relatively small, the results suggest that a reassessment of benzodiapine use may be required, with graded withdrawal being introduced as standard clinical practice even after very short periods of use. The efficacy of graded withdrawal will be assessed in the main study to follow.

6.2 I b) PILOT STUDY

A Controlled Comparison of Cognitive-Behaviour Therapy, Diazepam and Placebo in the Management of Generalised Anxiety Disorder in Primary Care.

As previously noted in the introductory chapters, the efficacy of psychological techniques in the management of GAD has been inconclusive, outcome results producing small improvements which are seldomly clinically significant (Ost 1982). As a consequence multidimensional and mixed-treatment approaches have been advocated (Mathews 1985) and recently adopted (Lindsay et al 1987; Blowers et al 1987; Butler et al 1987). Unfortunately, with the exception of Lindsay et al's (1987) study, the efficacy of multidimensional psychological treatments of GAD has yet to be adequately compared with widely used pharmacological alternatives.

In the present section of the pilot study a preliminary comparison of the relative effectiveness of CBT vs. diazepam vs. placebo in the management of GAD in a primary care setting was undertaken.

6.2.1 Subjects

The patient sample was as described in 6.1.1.

6.2.2 Treatments

Diazepam and placebo treatment groups were as described in section 6.1.2 and all patients were seen on an individual basis.

The CBT group received cognitive therapy based on Beck and Emery's (1979) approach which was specifically concerned with the elicitation and modification of automatic thoughts and irrational assumptions. Written handouts explaining the rationale and management techniques of cognitive therapy were given to patients (Appendix 5). In conjunction with the handouts,patients were also trained in progressive relaxation using a procedure adapted from Jacobson (1938). Patients were supplied with taped relaxation training instructions to be followed daily. Individual behavioural targets, such as graded exposure, were also set where necessary. The CBT approach used in the present study was similar to the "Anxiety Management" approach adopted by Butler et al (1987b) for the treatment of persistent generalised anxiety. Patients in the CBT group did not receive any concomitant psychotropic medication.

6.2.3 Procedure

All patients completed the initial GP baseline assessments, as outlined in section 6.1.3, before being randomly allocated to treatment groups. The procedure for diazepam and placebo treatment groups was as outlined in section 6.1.3. Patients allocated to the CBT group were seen for therapy on four occasions by the current author, who was not involved in the assessment of end of treatment outcome for the CBT group. Each CBT appointment for therapy lasted approximately fifty minutes. In addition CBT patients also received two fifteen-minute GP assessment appointments, and two psychologist assessor appointments,each conducted both prior to and

following treatment. CBT was provided over a six-week period, equivalent to the length of time diazepam and placebo patients received 'active' double-blind treatment. Following initial GP assessment, the diazepam and placebo groups received a one-week single-blind placebo wash-in period. No psychological or pharmacological treatment was given to the CBT group during this week.

The present author administered medication, and conducted treatment process and outcome assessments on the pharmacologically-treated patients and was certainly unaware of the drug status of the double-blind diazepam and placebo groups. Because the current author conducted the CBT it was thought methodologically unsatisfactory that he also should be responsible for asssessing treatment outcome for this group. So a psychologist assessor who was unaware of the nature of the study was asked to assess treatment outcome for the CBT group. However if informed by the patient the psychologist assessor could have concluded that a patient had been allocated to the CBT group. One therefore cannot presume that the psychologist assessor was completely blind when conducting outcome measures on the CBT group.

The psychologist assessor was trained in the administration of the HAM-A by the current author, prior to the commencement of this study. A sample of four non-study anxiety patients were independently rated on the HAM-A by the current author and the psychologist assessor. A high level of agreement on HAM-A scores was achieved (*Pearson* $r = 0.91$, $p < 0.01$).

6.2.4 Measures

Four primary measures of treatment process and outcome were used in this section of the pilot study.

a.) It is obviously not possible to determine how anxious patients in this study were in comparison to those reported in other studies given the probable variability in HAM-A scores between studies due to lack of specific severity criteria. In the present study GPs rated patients' severity of illness on a 7 - point scale at initial assessment and at the end of the active treatment period. The 7-point severity rating scale had four anchor points :

1 - normal; not at all ill, absence of symptoms

3 - mild; symptoms definitely present but no significant impairment of function

5 - moderate; a definite degree of impairment

7 - severe; an incapacitating condition.

b.) The Hamilton (1959) Rating Scale for Anxiety (HAM-A) and the Hamilton Anxiety Glossary (HAG) (Power et al 1985) were used as described in section 6.1.4 a). The HAM-A ratings were compared, for all three groups, at baseline pre-treatment (Day 0), one month following baseline (Day 28), and at the end of the active treatment period (Day 42).

c.) The Kellner and Sheffield (1973) Symptom Rating Test (SRT) was administered as described in section 6:1:4 b).

d.) Overall symptom change at the end of active treatment was assessed in all patients by GPs; for the diazepam and placebo groups by the current author; and for the CBT group by the

Psychologist Assessor. Patients were rated on a 7-point scale of overall symptom change, ranging from 1 - 'very much improved', 2 - 'much improved', 3 - 'minimally improved', 4 - 'no change', 5 - 'minimally worse', 6 - 'much worse' to 7 - 'very much worse'.

e) Finally, patients were seen at 12-month follow-up, and GP records were examined to assess subsequent post-study psychotropic medication usage, and psychological or psychiatric treatment. The clinical assessment at follow-up is not reported, as it was impossible to ascertain what factors were responsible for clinical status given the possible confounding influence of subsequent post-study treatment.

6.2.5 Results

Of the patients assessed by GPs at initial inteview, on the 1 - 7 severity scale, 16% were given a rating of 3 (mild); 21% a rating of 4; 58% a rating of 5 (moderate); and 5% a rating of 6. There were no significant differences between treatment groups in terms of GP initial severity ratings.

One-way analyses of variance were performed between groups on the pre-treatment SRT and HAM-A ratings, and also on the subjects' demographic variables, ie. age and duration of symptoms (see Table 6.1). No significant results were obtained, suggesting that the three treatment groups were comparable prior to treatment. Table 6.5 gives the means and standard deviations for each group at each assessment on the SRT and the HAM-A.

Effects of treatment were investigated by computing repeated

measures analyses of variance (MANOVA) with treatment group as the between-subjects factor and time of assessment as the within-group factor.

a.) HAM-A ratings : The between-group analyses revealed a significant time ($F(2,56) = 82.3$, $p < 0.05$) and interaction effect ($F(4,56) = 7.2$, $p < 0.05$), with no significant group effect. Within-group repeated measures MANOVA over the three assessment sessions showed significant change during treatment for the placebo ($F(2,20) = 5.21$, $p < 0.05$), diazepam ($F(2,18) = 22.07$, $p < 0.0005$), and CBT ($F(2,18) = 185.02$, $p < 0.0005$) groups. The only significant difference between treatment groups was at the end of active treatment (day 42) ($F(2,28) = 5.16$, $p < 0.05$). A post-hoc Scheffe test indicated a significant difference between CBT and placebo groups at the 0.05 level.

b.) SRT ratings : A between-group analysis produced a significant time effect ($F(2,56) = 13.6$, $p < 0.05$) with no significant group or interaction effect. Within-group repeated measures MANOVA over the three assessment sessions showed that only the CBT group changed significantly during treatment ($F(2,18) = 31.35$, $p < 0.0005$), but no significant differences between treatment groups occurred on any of the individual assessment days.

c.) Overall symptom change : While the above results establish levels of statistical significance in group comparisons using specific anxiety measures, an assessment by GP and psychologist assessors, of symptom change at the end of active treatment period (day 42) illustrates clinically-rated change. Table 6.6 shows

patients' symptom change at day 42 in comparison to study entry, and also reveals the high level of agreement between GP and psychologist assessors (Pearson r = 0.89, p <0.005).

d.) Follow-up : Recent studies have noted an inability to collect adequate follow-up data as patients often require subsequent treatment between the end of the active study period and the designated follow-up date (Tarrier and Main 1986; Lindsay et al 1987). Bellack and Hersen (1984) recommend the use of 'unobtrusive measures' at follow-up to extend the external validity of research findings, and to reduce contamination effects of subsequent treatment. Table 6.7 illustrates post-study psychotropic prescription and / or psychological treatment at twelve months follow-up.

Table 6.5. Means and standard deviations (SD) for each group at each assessment session during treatment on the HAM-A and SRT.

	CBT		Diazepam		Placebo	
HAM-A	$\bar{X}$	(SD)	$\bar{X}$	(SD)	$\bar{X}$	(SD)
Day 0	18.1	(2.5)	18.9	(3.7)	16.7	(1.1)
Day 28	7.8	(4.1)	11.0	(7.3)	12.7	(6.3)
Day 42	4.5	(4.6)	9.9	(6.3)	12.6	(6.3)
SRT						
Day 0	31.0	(9.3)	37.1	(12.0)	34.7	(9.7)
Day 28	17.0	(10.3)	30.4	(18.0)	28.3	(16.0)
Day 42	14.4	(12.1)	26.1	(17.3)	27.1	(16.6)

Table 6.6. GP and psychologist assessor (PA) ratings of overall symptom change at end of active treatment period.

Symptom Change	GP			PA		
	CBT	DZ	PL	CBT	DZ	PL
Very much improved	6	2	-	6	2	2
Much improved	4	4	5	3	4	4
Minimally improved	-	3	2	1	2	1
No change	-	-	2	-	1	1
Minimally worse	-	1	1	-	1	1
Much worse	-	-	1	-	-	1
Very much worse	-	-	-	-	-	-

Table 6.7. Subsequent psychological and / or psychotropic treatment at 12 months follow-up.

	CBT (N = 10)	Diazepam (N = 10)	Placebo (n = 11)
Psychological	-	3	4
Psychotropic	3	2	1
Psychological + Psychotropic	-	2	1

6.2.6 Discussion

Using the more restricted number of within-group assessments over time, (in comparison to Pilot Study 1a), results of the HAM-A ratings support a significant treatment effect for all three groups. The end of treatment CBT scores were significantly lower than placebo, but no such difference existed between diazepam and placebo groups. Results of the SRT scores suggest a significant improvement over time for the CBT group alone, although there were no significant differences between treatment groups on any of the individual assessment days. A non-significant trend for a reduction in self-report symptoms was evident in the diazepam and placebo groups. Large standard deviation in the SRT ratings of all three groups (Table 6.3) illustrate the wide range of patients' self-report anxiety symptoms prior to and following treatment.

End of therapy assessments were conducted prior to diazepam withdrawal so that outcome results were not confounded by the withdrawal symptoms or anxiety recurrence that may develop following cessation of benzodiazepine treatment (Pilot Study 1a).

In general there existed close agreement between the GP and psychological assessment of the proportion of patients in each category of symptom change following treatment. For both GPs and psychological assessor there existed a greater spread of treatment response for diazepam and placebo groups than for the CBT group. This may reflect the greater range of SRT and HAM-A ratings at the end of treatment for diazepam and placebo groups than for the CBT group. Some researchers note the need for further treatment of

patients following the end of study treatment period (Tarrier and Main 1986), and others state that virtually no patients are symptom-free at follow-up (Durham and Turvey 1987). At twelve months follow-up three of ten CBT patients had received subsequent psychotropic medication. This may suggest that the study period was too short and amount of CBT inadequate. The treatment period has therefore been extended in the main study to follow. Seven of ten diazepam patients received subsequent psychotropic and /or psychological treatment. This high proportion may have been inadvertently inflated by placebo substitution withdrawal from diazepam and the subsequent recurrence of anxiety or withdrawal symptoms, or a lack of satisfaction with the degree of improvement during diazepam treatment. In order to minimize the impact of withdrawal symptoms at treatment outcome and follow-up, placebo substitution graded withdrawal,will be adopted in the main study to follow. At the end of active treatment the placebo group achieved the smallest degree of symptom improvement on both the HAM-A and SRT ratings and unsurprisingly six of eleven patients received subsequent treatment.

It is important to note that there was no formal assessment of CBT content or skill of the current author as therapist. The degree of contact involved in assessing cognitive and psychomotor performance of the diazepam and placebo groups was the same as that given to the CBT group. This reduces the possibility that the comparatively greater improvement in the CBT group at the end of active treatment could be attributed to the amount of psychologist

attention patients received. This factor was seldom controlled for in other studies. However since the diazepam and placebo groups received no direct form of counselling, it would be inappropriate to claim that the superiority of CBT was related to the technique itself rather than to it simply being a structured form of counselling intervention. Furthermore the psychomotor assessments conducted on the diazepam and placebo groups could possibly have had an adverse impact on treatment outcome. So in the main study to follow, patient groups will continue to be balanced for overall amount of psychologist contact but the patients receiving diazepam alone and placebo alone will not undergo psychomotor assessment, but will simply receive enquiries about response to treatment, conducted in a non-directive manner, so as to avoid making suggestions of a therapeutic nature.

It could be argued that in the absence of a waiting-list control group, it is not possible to be certain that change over time was attributable to treatment per se. However, Lindsay et al (1987), Blowers et al (1987), and in particular Butler et al (1987a) all reported the superiority of a form of psychological treatment similar to that adopted in the present study, in comparison to waiting-list controls.

Although the pilot studies suggest the superiority of CBT over diazepam and placebo as treatment for GAD, the results do not permit a wholly adequate comparison of treatment efficacy at follow-up. In addition there was no combined psychological and pharmacological treatment group, and the number of outcome

measures, and sample size merit expansion.

Results of this section of the Pilot Study are currently in press (Power et al. 1989).

The main study attempts to redress most of the pilot study inadequacies, and to extend the area of inquiry.

CHAPTER 7 : MAIN STUDY

7.1 A Controlled Comparison of the Efficacy of Diazepam, Placebo, Cognitive-Behaviour Therapy, Diazepam plus Cognitive-Behaviour Therapy, and Placebo plus Cognitive-Behaviour Therapy in the Management of Generalised Anxiety Disorder in Primary Care.

This main study attempts to redress many of the methodological inadequacies of previous studies, cited in the introductory chapters, that investigated the efficacy of pharmacological treatments and/or psychological approaches in the management of GAD. In addition lessons from the Pilot Study (Chapter 6) have also been incorporated in the design and method of the main study. This study attempts to compare the efficacy of diazepam (DZ) vs. placebo (PL) vs. cognitive behaviour therapy (CBT) vs. diazepam plus cognitive-behaviour therapy (DZ+CBT) vs. placebo plus cognitive-behaviour therapy (PL+CBT) in the management of primary care GAD patients who are drug-free at time of referral, and who are not using non-study concomitant psychotropic medication during the course of study treatment.

7.1.1 Subjects

Patients presenting to general practitioners (GP) with GAD who were thought suitable for pharmacological and/or psychological treatment were referred for study inclusion. Following GP

assessment of psychological morbidity the present author then assessed patient characteristics, present mental state, and severity of illness. Patients were considered suitable for study inclusion if they met the same detailed criteria outlined in the Pilot Study (section 6.1.1.). A total of 113 patients were referred by GPs for study inclusion. One patient was not included as their anxiety state was not of adequate severity to meet entry criteria. One patient was not admitted to the study following the use of concomitant non-study prescribed benzodiazepines. Two patients failed to attend for initial psychological assessment. A further five patients dropped-out after initial psychological assessment, and the attendance of 3 other patients was so sporadic that few relevant data were available, and so they were excluded from analysis. A total of 101 patients were included in the study.

7.1.2 Treatments

The 101 patients received one of five treatments: diazepam (DZ) (n = 22), placebo (PL) (n = 19), cognitive-behaviour therapy (CBT) (n = 21), diazepam plus cognitive-behaviour therapy (DZ + CBT) (n = 21), placebo plus cognitive-behaviour therapy (PL + CBT) (n = 18). All patients were treated on an individual basis by the present author.

7.1.2.1 Diazepam Therapy (DZ)

a) Wash-In: Patients were initially placed on one-week, single-

blind, placebo, three times daily.

b) Active-Treatment: Following wash-in patients received six weeks double-blind diazepam, three times daily (5mg + 5mg + 5mg).

c) Graded-Withdrawal: At the end of active-treatment patients received one-week, double-blind diazepam plus placebo substitution three times daily (5mg + placebo + 5mg), followed by another one-week double-blind diazepam plus placebo substitution (placebo + placebo + 5mg). Patients were then continued single blind on placebo three times daily for a final one-week period.

7.1.2.2 Placebo Therapy (PL)

a.) Wash-In : Patients were initially placed on one-week single-blind placebo three times daily (as in section 7.1.2.1.(a)).

b.) Active-Treatment : Following wash-in, patients received six weeks double-blind placebo, three times daily.

c.) Graded-Withdrawal : At the end of active-treatment, patients received two weeks double-blind placebo three times daily. Patients were then continued single-blind on placebo three times daily for a final one-week period.

7.1.2.3 Cognitive-Behaviour Therapy (CBT)

All patients received a maximum of seven CBT treatment sessions which utilized the same methods as the Pilot Study (section 6.2.2). CBT treatment sessions were provided over a nine-week period equivalent to the length of time DZ and PL groups received double-blind active-treatment and graded withdrawal.

7.1.2.4 Diazepam plus Cognitive-Behaviour Therapy (DZ + CBT)

a) Wash-In: As in section 7.1.2.1.(a).

b) Active-Treatment: Six weeks double-blind diazepam (5mg t.i.d) as in section 7.1.2.1.(b). Patients also received a maximum of seven CBT sessions as in section 7.1.2.3. (over the equivalent nine weeks encompassing active-treatment and graded-withdrawal periods).

c) Graded-Withdrawal: As in section 7.1.2.1.(c).

7.1.2.5 Placebo plus Cognitive-Behaviour Therapy (PL + CBT)

a.) Wash-In : As in section 7.1.2.1.(a).

b.) Active-Treatment : Six weeks double-blind placebo (t.i.d) as in section 7.1.2.2.(b). Patients also received a maximum of seven CBT sessions as in section 7.1.2.3 (over the equivalent nine weeks encompassing active-treatment and graded-withdrawal periods).

c.) Graded-Withdrawal : As in section 7.1.2.2.(c).

7.1.3 Procedure

Following the initial GP assessment (day - 7), patients were randomly allocated to treatment groups. After completion of the one-week wash-in period, or equivalent for the CBT alone group, all patients completed baseline psychological assessment (day 0), conducted by the present author. Thereafter all drugs, packaged in identical bubble-packs, were dispensed by the present author. Only enough medication to last to the next scheduled appointment was dispensed at any one time, and bubble-packs were returned at

each assessment to check compliance.

Over the six-week double-blind drug period the DZ and PL patients were seen individually on five occasions by the present author (days 0, 7, 14, 28, 42,). At the end of active double-blind treatment DZ and PL patients continued double-blind graded-withdrawal and were again seen by the present author at the end of this two-week period (day 56). Patients then completed graded-withdrawal with one-week single-blind placebo and were assessed by the present author at the end of this period (day 63). Finally one week after ceasing all medication (day 70) patients were assessed by the present author and their respective GPs. In total patients were seen on eight occasions by the current author and twice by their GPs. For DZ and PL patients the present author assessed drug compliance, adverse symptoms, and inquired about response to treatment in a non-directive manner so as to avoid making suggestions of a therapeutic nature (as in section 6.1.3). Consequently each DZ and PL patient received approximately 5 hours and 40 minutes contact with the present author and 30 minutes GP assessment contact.

Patients allocated to CBT alone were seen individually for therapy by the current author according to the same time schedule as the DZ and PL patients. Each CBT appointment for therapy lasted approximately 40 minutes. In addition CBT patients also received two 15-minute GP assessments. The CBT group received no psychotropic medication at any time during the study period. The DZ + CBT group, and the PL + CBT group both received psychotropic

medication and individual therapy, administered by the current author, according to the same time schedule as the DZ, PL, and CBT alone groups. All groups received approximately the same amount of contact with the current author and their respective GPs.

7.1.4 Measures

Seven primary measures of treatment process and outcome were used in this main study.

a) The Hamilton (1959) Rating Scale for Anxiety (HAM-A) with the Hamilton Anxiety Glossary (HAM-G) (Power et al 1985) as described in section 6.1.4.(a). The HAM-A was completed for all groups on Days 0, 7, 14, 28, 42,, 56, 63 and 70.

b) The Kellner and Sheffield (1973) Symptom Rating Test (SRT) as described in section 6.1.4.b. The SRT was completed by patients on Days -7, 0, 7, 14, 28, 42, 56, 63 and 70.

c) The General Health Questionnaire (Goldberg 1972) (Appendix 6) is a well-known and extensively validated screening method for the identification of psychiatric illness in general practice. It has been tested and validated in a number of cultures and languages (eg. Harding 1976; Munoz et al 1978; Chan and Chan 1983). The version of the GHQ used in this study consisted of 60 items with four response categories each. Conventionally each item is scored by setting codes 1 and 2 to 0, and 3 and 4 to 1. Johnstone and Goldberg (1976) suggested that respondents with scores of between 12 and 19 tend to remit with time, even without treatment; but those with scores of 20 or more

tend to improve only if offered treatment. The GHQ was completed by patients at Days 0 and 70.

d) A 10cm 'Tense-Relaxed' visual analogue scale (Appendix 7), relating to the previous week, and anchored at end points 0 = Relaxed, 10 = Tense, was completed by patients according to the same schedule as the SRT in section 7.1.4.(b).

e) At Day 0 patients were asked what symptom particularly bothered them. There were no preconditions or restrictions on the patients' reply and their answer was regarded as their personal main 'Target Symptom'. Patients were subsequently asked to complete a 10cm 'Target Symptom' visual analogue scale (Appendix 8), relating to the previous week and anchored at end points 0 = Not at all bothered; 10 = Extremely bad, could not be worse. The Target Symptom visual analogue scale was completed according to the same schedule as the HAM-A in section 7.1.4.(a)

f) Severity of Illness was rated on a 7 - point scale, as described in section 6.2.4.(a), by GPs at Day -7 and Day 70. The current author also rated Severity of Illness on the same 7 - point scale, according to the same schedule as the HAM-A in section 7.1.4.(a).

g) Overall Symptom Change was assessed on a 7 - point scale, as described in section 6.2.4.(d)., by GPs at Day 70. Patients also rated Overall Symptom Change on the same 7 - point scale, according to the same schedule as the HAM-A in section 7.1.4.(a). The current author also completed the same 7 - point scale for each patient on Days 7, 14, 28, 42, 56, 63 and 70.

h) In addition adverse reactions to the drug regimen were recorded by the present author at each assessment interview by means of an open-ended interview and check-list of adverse symptoms as in 6.1.4.(c).

i.) Finally patients were seen at 6 months follow-up and GP records were examined to assess subsequent post-study psychotropic medication usage and psychological or psychiatric treatment. In addition patients completed the SRT, GHQ, 'Tense-Relaxed', and 'Target Symptom' visual analogues, and self-reported Overall Symptom Change. The current author also completed the HAM-A, Severity of Illness and Overall Symptom Change.

7.1.5. Results

The main demographic details of patients included in this study are as shown in Table 7.1.

One-way analyses of variance between groups failed to produce any significant differences with regard to age ($F(4,96) = 0.823$ $p = 0.513$); duration of symptoms ($F(4,96) = 0.028$, $p = 0.998$); Day -7 SRT ($F(4,96) = 0.11$, $p = 0.976$); Day 0 HAM-A ($F(4,96) = 0.33$, $p = 0.856$); Day -7 'Tense-Relaxed' visual analogue ($F(4,96) = 0.31$, $p = 0.864$); Day 0 'Target Symptom' visual analogue ($F(4,96) = 0.74$, $p = 0.561$); and Day 0 GHQ ($F(4,96) = 0.31$, $p = 0.868$); thereby suggesting that the groups were comparable prior to active treatment.

Effects of treatment were investigated by computing repeated measures analyses of variance (MANOVA) with treatment group as the

Table 7.1 Demographic features of Main Study GAD patients.

	DZ (n=22)	PL (n=19)	CBT (n=21)	DZ+CBT (n=21)	PL+CBT (n=18)
Mean Age (yrs)	39.77	42.57	41.47	36.33	42.38
Sex	6M,16F	3M,1F	8M,13F	7M,14F	5M,13F
Duration of symptoms (mths)	3.36	3.31	3.19	3.28	3.27
Nos patients previously prescribed benzo-diazepines	17	16	19	16	10
Nos patients previously referred for psychological or psychiatric treatment	5	6	7	5	6

between-subjects factor and time of assessment as the within-group factor. Tests for simple effects were then carried out with a priori or post-hoc comparisons where appropriate.

a) HAM-A rating: Table 7.2 presents the HAM-A means and standard deviations for each treatment group at each assessment stage during treatment and Figure 3 illustrates the data graphically.

The between-group analysis revealed a significant group ($F(4,96) = 4.75$, $p < 0.005$), time ($F(7,672) = 180.48$, $p < 0.001$) and interaction effect ($F(28,672) = 7.78$, $p < 0.001$), indicating differential changes across groups. An analysis of F tests for simple effects was carried out for each time of assessment, with post-hoc Scheffe tests to illustrate specific between group differences and the results are to be found summarised in Table 7.3. No significant between-group HAM-A differences emerged until Day 28 when PL and DZ + CBT groups were the first to significantly differ. This difference was maintained throughout the remainder of the study period. On Day 42 a significant difference between DZ and DZ + CBT, and between PL and CBT groups emerged and was again maintained at subsequent assessments. At Day 63 DZ and CBT groups differed for a singular occasion as did PL and PL + CBT on Day 70. At no time did CBT, DZ + CBT and PL + CBT groups differ from each other. Similarly, at no time were DZ and PL groups, or DZ and PL + CBT groups significantly different. The above results illustrate differences between the treatment groups in the rate of change. Within-group analysis revealed a

Table 7.2 HAM-A means and standard deviations (SD) for treatment groups at each assessment stage during treatment.

HAM-A	DZ	PL	CBT	DZ+CBT	PL+CBT
Day 0	18.7 (3.7)	17.8 (2.4)	18.5 (3.1)	18.9 (5.1)	17.9 (2.6)
Day 7	12.9 (5.0)	14.5 (4.9)	14.5 (3.7)	12.5 (4.0)	15.3 (3.3)
Day 14	11.1 (6.2)	13.3 (5.9)	11.4 (4.5)	8.9 (4.7)	11.4 (5.3)
Day 28	10.3 (5.8)	13.0 (6.1)	9.0 (5.0)	7.0 (4.2)	10.0 (5.8)
Day 42	10.9 (7.5)	13.4 (5.7)	7.6 (5.0)	5.1 (3.3)	7.8 (5.5)
Day 56	10.5 (7.0)	13.0 (6.2)	5.7 (4.4)	4.3 (3.2)	7.3 (5.4)
Day 63	10.6 (7.0)	12.8 (6.2)	5.1 (4.7)	4.4 (4.2)	7.1 (5.5)
Day 70	10.5 (7.0)	12.9 (6.2)	5.2 (4.8)	4.0 (4.2)	7.0 (5.4)

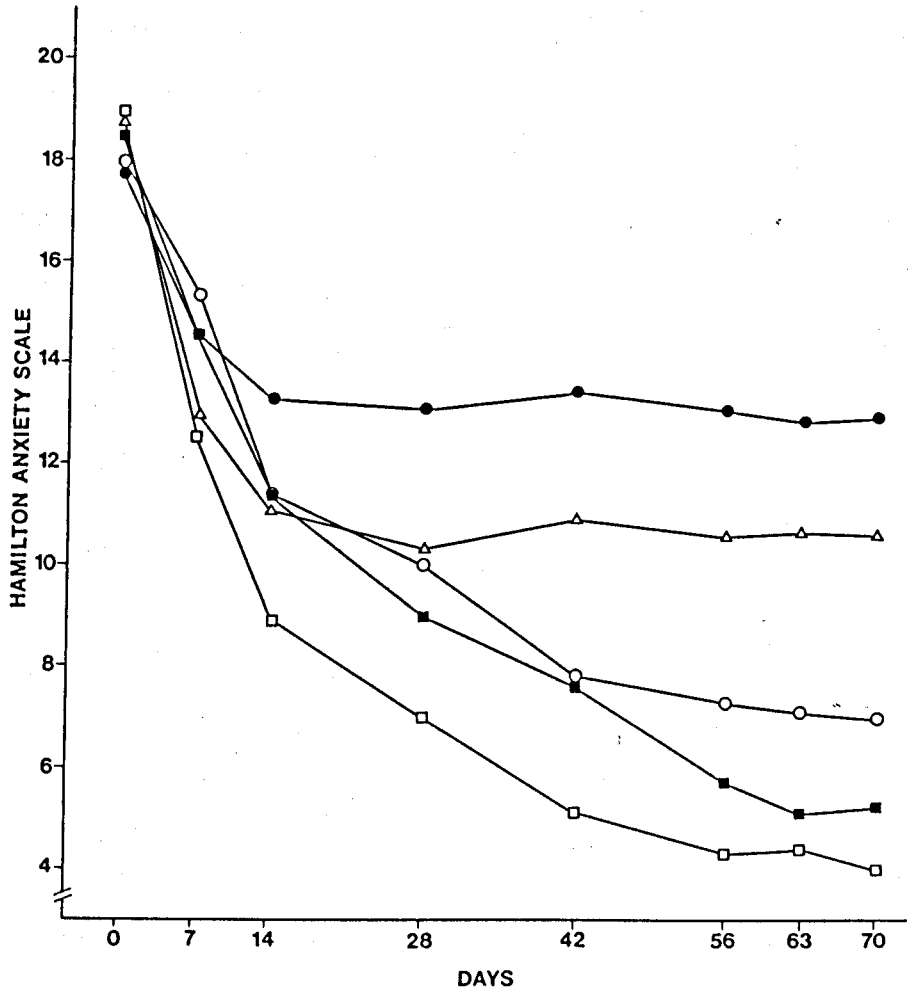

FIG. 3 Mean Hamilton Anxiety Scale scores for treatment groups at each assessment stage during treatment:
△ DZ; ● PL; ■ CBT; □ DZ+CBT; ○ PL+CBT.

Table 7.3 Analysis of variance and simple effects on Hamilton Anxiety Scale Scores at each assessment stage during treatment.

(i) Two factor ANOVA with repeated measures on B.	df	F	p
Factor A (treatment group)	4,96	4.75	0.002**
Factor B (time of assessment)	7,672	180.48	0.000***
Interaction A X B	28,672	7.78	0.000***

(ii) Simple effects (SS, Factor A)

	df	F	p	Scheffe
Day 0	4,96	0.33	0.856	
Day 7	4,96	1.59	0.181	
Day 14	4,96	1.72	0.150	
Day 28	4,96	3.25	0.015*	2-4*
Day 42	4,96	6.63	0.0001***	1-4*, 2-3*,2-4***
Day 56	4,96	8.39	0.0000***	1-4*, 2-3**,2-4***
Day 63	4,96	8.16	0.0000***	1-3*,1-4*,2-3**,2-4***
Day 70	4,96	8.71	0.0000***	2-5*,1-4**,2-3**,2-4***

(iii) Simple Effects (SS, Factor B)

DZ	7,672	23.94	0.000***
PL	7,672	7.35	0.000***
CBT	7,672	66.08	0.000***
DZ + CBT	7,672	75.89	0.000***
PL + CBT	7,672	41.20	0.000***

* p <0.05; ** p <0.01; *** p < 0.001

Key : Post-hoc Scheffe treatment group comparisons :- 1 = DZ; 2 = PL; 3 = CBT; 4 = DZ + CBT; 5 = PL + CBT

Note : Groups separated by a hyphen differ significantly from each other.

significant reduction in HAM-A scores for all groups during the course of treatment (see Table 7.3).

There was no significant increase in HAM-A scores for the DZ and DZ + CBT groups during the course of graded-withdrawal from Day 42 to 63 ($t = 1.10$, $df = 21$, $p = 0.284$; $t = 0.91$, $df = 20$, $p = 0.373$), or following cessation of all tablet consumption between Days 63 and 70 ($t = 0.38$, $df = 21$, $p = 0.704$; $t = 1.57$, $df = 20$, $p = 0.131$). The absence of an increase in HAM-A scores during or after graded-withdrawal is of major clinical importance. Comparison of pre- (Day 0) and post-treatment (Day 70) HAM-A scores revealed a significant reduction for DZ ($t = 5.93$, $df = 21$, $p < 0.001$), CBT ($t = 13.97$, $df = 20$, $p < 0.001$), DZ + CBT ($t = 11.01$, $df = 20$, $p < 0.001$), PL + CBT ($t = 8.34$, $df = 17$, $p < 0.001$) groups and to a less extent the PL group ($t = 3.83$, $df = 18$, $p < 0.005$).

b) SRT ratings : Table 7.4 presents the SRT means and standard deviations for each treatment group at each assessment stage during treatment and Figure 4 illustrates the data graphically. The between-group analysis (Table 7.5) revealed a significant group ($F(4,96) = 2.79$, $p < 0.05$), time ($F(8,768) = 103.04$, $p < 0.001$), and interaction effect ($F(32,768) = 4.73$, $p < 0.001$) indicating differential changes across groups. F tests for simple effects and post-hoc Scheffe tests revealed no significant between group differences until Day 42 when PL and DZ + CBT were the first to significantly differ. This difference was maintained throughout the remainder of the study. On Day 56 and thereafter significant differences between DZ and DZ + CBT, and

Table 7.4 SRT means and standard deviations (SD) for treatment groups at each assessment stage during treatment.

SRT	DZ	PL	CBT	DZ+CBT	PL+CBT
Day -7	39.3 (14.4)	40.2 (8.1)	39.4 (15.0)	39.7 (13.3)	41.7 (10.0)
Day 0	36.6 (13.6)	38.1 (8.5)	39.9 (15.8)	39.7 (13.4)	39.4 (10.4)
Day 7	28.0 (12.8)	32.8 (15.4)	32.5 (16.6)	27.4 (11.5)	34.1 (12.2)
Day 14	25.5 (13.2)	31.5 (16.7)	25.6 (15.0)	19.6 (10.7)	26.0 (18.3)
Day 28	24.8 (13.3)	30.3 (18.0)	20.9 (14.5)	18.6 (13.8)	22.3 (14.0)
Day 42	26.3 (15.7)	30.4 (17.5)	18.0 (13.9)	13.6 (10.5)	19.6 (14.9)
Day 56	25.6 (14.6)	30.3 (18.0)	13.3 (11.5)	11.9 (9.4)	17.7 (11.9)
Day 63	24.8 (15.2)	29.5 (18.4)	12.6 (12.6)	10.3 (10.7)	17.4 (12.5)
Day 70	24.8 (15.7)	30.0 (18.4)	12.5 (13.9)	9.9 (10.4)	16.8 (11.7)

Table 7.5 Analysis of variance and simple effects on Kellner and Sheffield (SRT) scores at each assessment stage during treatment.

(i) Two-factor ANOVA with repeated measures on B.	df	F	p
Factor A (treatment group)	4,96	2.79	0.031*
Factor B (time of assessment)	8,768	103.24	0.000***
Interaction A X B	32,768	4.73	0.000***

(ii) Simple effects (SS, Factor A)

	df	F	p	Scheffe
Day -7	4,96	0.11	0.976	
Day 0	4,96	0.24	0.913	
Day 7	4,96	0.97	0.427	
Day 14	4,96	1.58	0.184	
Day 28	4,96	1.81	0.132	
Day 42	4,96	4.20	0.003**	2-4*
Day 56	4,96	7.12	0.0000***	1-4*,2-3**,2-4**
Day 63	4,96	6.63	0.0001***	1-4*,2-3**,2-4**
Day 70	4,96	6.98	0.0001***	1-4*,2-3**,2-4**

(iii) Simple effects (SS, Factor B)

DZ	8,768	10.05	0.000***
PL	8,768	4.29	0.000**
CBT	8,768	38.64	0.000***
DZ + CBT	8,768	43.92	0.000***
PL + CBT	8,768	25.98	0.000***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Key : Post-hoc Scheffe treatment group comparisons :- 1 = DZ; 2 = PL; 3 = CBT; 4 = DZ + CBT; 5 = PL + CBT

Note : Groups separated by a hyphen differ significantly from each other.

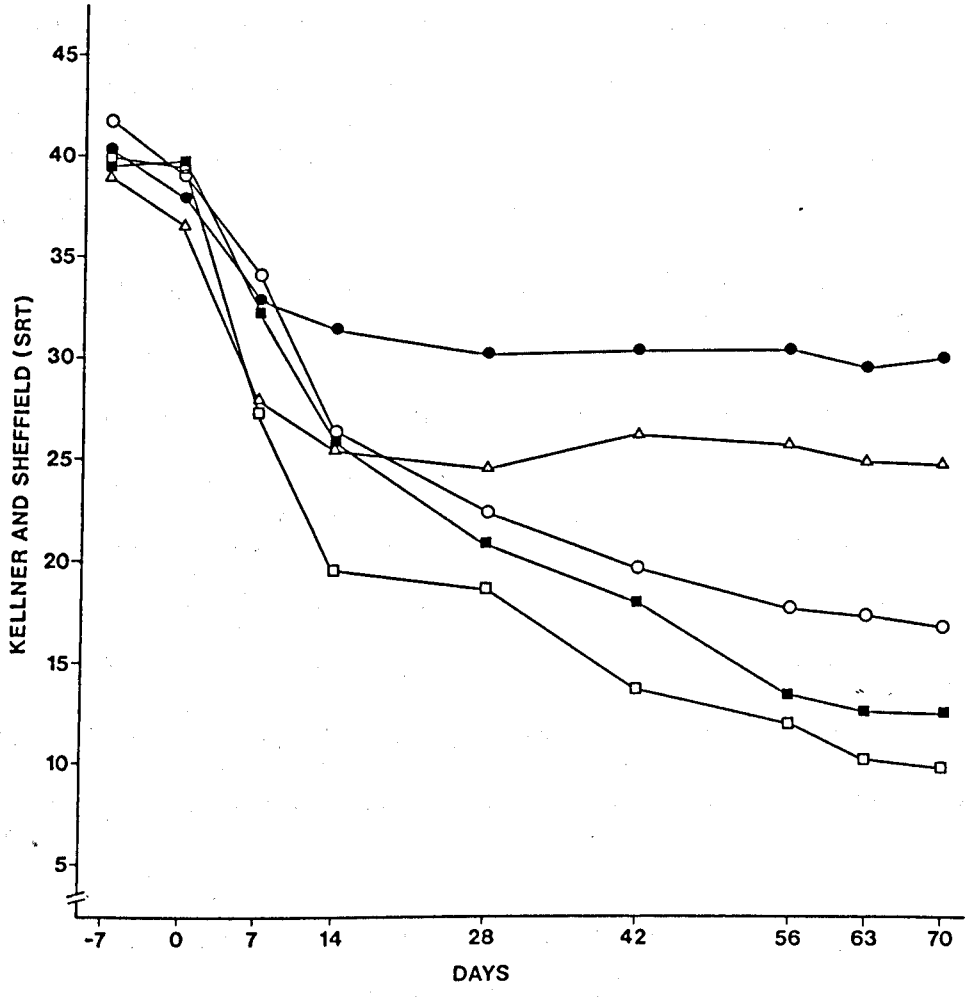

FIG. 4 Mean Kellner and Sheffield (SRT) scores for treatment groups at each assessment stage during treatment:
△ DZ; ● PL; ■ CBT; □ DZ+CBT; ○ PL+CBT.

between PL and CBT groups were evident. There were no other between-group differences. Table 7.5 also illustrates the significant reduction in SRT scores for all treatment groups during the study period. Within-group analysis also revealed that only the PL group showed a significant reduction in symptoms during the initial single-blind placebo wash-in period ($t = 2.26$, $df = 18$; $p < 0.05$). There was no significant increase in SRT scores for the DZ and DZ + CBT groups during the course of graded-withdrawal from Day 42 to 63 ($t = 1.82$, $df = 21$, $p = 0.084$; $t = 1.33$, $df = 20$, $p = 0.197$) or following cessation of all tablet consumption between Days 63 and 70 ($t = 0.00$, $df = 21$, $p = 1.000$; $t = 0.38$, $df = 20$, $p = 0.710$). Comparison of pre (Day -7) and post (Day 70) SRT scores revealed a significant reduction for DZ ($t = 4.21$, $df = 21$, $p < 0.001$), CBT ($t = 8.57$, $df = 20$, $p < 0.001$), DZ + CBT ($t = 8.27$, $df = 20$, $p < 0.001$), PL + CBT ($t = 6.89$, $df = 17$, $p < 0.001$) groups, and to a less extent the PL group ($t = 2.65$, $df = 18$, $p < 0.05$).

c) GHQ ratings : Table 7.6 presents GHQ total and subscale means and standard deviations for each treatment group prior to active treatment at Day 0, and post-treatment at Day 70.

In order to assess the significance of GHQ change displayed by the groups over time, paired t-tests were conducted. The results of these are shown in Table 7.7.

As can be seen the PL group stands out as the one group that made no significant changes between the two testings on the GHQ-Total, and only showed a significant change on the Anxiety/Insomnia

Table 7.6. GHQ Total and Subscale means and standard deviations (SD) for treatment groups at Day 0 and Day 70.

	DZ	PL	CBT	DZ+CBT	PL+CBT
GHQ	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)
Total					
Day 0	39.40(8.74)	39.89(9.86)	39.61(10.16)	38.23(12.07)	36.50(12.30)
Day 70	27.00(16.46)	31.94(17.25)	11.38(16.82)	7.95(12.44)	16.11(15.91)
Somatic Symptoms					
Day 0	5.18(1.84)	5.21(1.71)	4.95(2.08)	4.95(1.98)	4.50(2.14)
Day 70	3.54(2.57)	4.00(2.47)	1.28(1.76)	0.90(1.72)	2.00(2.30)
Anxiety + Insomnia					
Day 0	6.45(0.67)	6.36(0.76)	6.04(1.11)	6.33(0.96)	6.33(1.08)
Day 70	5.09(2.24)	5.21(2.34)	1.95(2.57)	1.66(1.90)	2.94(2.41)
Social Dysfunction					
Day 0	4.18(1.40)	4.42(1.53)	4.85(1.42)	4.71(1.92)	4.16(1.94)
Day 70	2.68(2.23)	3.57(2.31)	1.47(2.33)	0.71(1.73)	2.00(2.24)
Severe Depression					
Day 0	2.50(2.04)	2.73(1.85)	2.95(2.90)	2.38(2.34)	2.27(2.32)
Day 70	1.04(2.10)	1.94(2.17)	0.85(2.05)	0.38(1.53)	1.05(2.15)

Table 7.7. GHQ Total and Subscale Paired t-tests at Day 0 and Day 70 for treatment groups.

	DZ	PL	CBT	DZ+CBT	PL+CBT
	df = 21	df = 18	df = 20	df = 20	df = 17
GHQ	t	t	t	t	t
Total	4.08**	2.10	8.33***	9.29***	5.46***
Somatic Symptoms	3.12**	2.00	6.90***	7.67***	3.86**
Anxiety + Insomnia	2.92**	2.32*	7.54***	9.63***	5.75***
Social Dysfunction	3.71**	1.49	7.35***	8.74***	4.65***
Severe Depression	3.42**	1.87	3.74**	4.19***	1.85

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Subscale. The PL + CBT group achieved significantly lower scores on the GHQ Total and two of the subscales. However the DZ, CBT, and DZ + CBT groups exhibited consistently lower scores on all measures. The magnitude of the difference between the day 0 and day 70 tended to be greater for the CBT and DZ + CBT groups.

There was no significant difference in GHQ Total and Subscale scores between treatment groups at Day 0 as illustrated in Table 7.8. However at Day 70 the GHQ Total differed significantly between DZ and CBT, PL and CBT, DZ and DZ +CBT, and PL and DZ + CBT groups. These differences were also present for Somatic Symptoms, and Anxiety and Insomnia Subscales. The Social Dysfunction Subscale revealed a significant difference only between PL and DZ + CBT groups.

d) 'Tense-Relaxed' visual analogue. Table 7.9 presents the 'Tense-Relaxed' visual analogue means and standard deviations for each treatment group at each assessment stage during treatment.

The between-group analysis revealed a significant group ($F(4,96) = 6.35$, $p < 0.001$), time ($F(8,768) = 68.80$, $p < 0.001$) and interaction effect ($F(32,768) = 4.81$, $p < 0.001$) indicating differential changes across groups. Significant differences between groups first emerged at Day 14 when PL differed from both CBT and DZ + CBT groups. This difference persisted for the duration of the study period. At Day 56 and thereafter PL and PL + CBT groups differed. DZ and CBT groups differed at Day 63 and Day 70. The above 'Tense-Relaxed' results are illustrated in Table 7.10.

Table 7.8. One-way analysis of variance on GHQ Total and Subscales at Day 0 and Day 70 for treatment groups.

Day 0	df	F	p	Scheffe
GHQ Total	4,96	0.31	0.868	
Somatic Symptoms	4,96	0.39	0.811	
Anxiety + Insomnia	4,96	0.57	0.683	
Social Dysfunction	4,96	0.72	0.578	
Severe Depression	4,96	0.34	0.846	
Day 70				
GHQ Total	4,96	8.47	0.0000***	1-3*,2-3**,1-4**,2-4***
Somatic Symptoms	4,96	7.95	0.0000***	1-3*,2-3**,1-4**,2-4**
Anxiety + Insomnia	4,96	11.11	0.0000***	1-3**,2-3**,1-4***,2-4***
Social Dysfunction	4,96	5.12	0.0009***	2-4**
Severe Depression	4,96	1.57	0.187	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Key : Post-hoc Scheffe treatment group comparisons :- 1 = DZ; 2 = PL; 3 = CBT; 4 = DZ + CBT; 5 = PL + CBT

Note : Groups separated by a hyphen differ significantly from each other.

Table 7.9. 'Tense-Relaxed' visual analogue means and standard deviations (SD) for treatment groups at each assessment stage during treatment.

Tense-Relaxed visual analogue	DZ	PL	CBT	DZ+CBT	PL+CBT
Day -7	7.72 (2.25)	7.89 (1.32)	8.09 (1.33)	7.76 (1.33)	8.16 (1.15)
Day 0	6.77 (2.34)	7.78 (1.39)	7.57 (2.37)	7.81 (1.40)	8.05 (1.25)
Day 7	5.40 (2.17)	6.31 (2.68)	6.04 (2.17)	5.61 (2.73)	7.83 (1.68)
Day 14	4.90 (2.50)	7.00 (2.21)	4.61 (2.20)	4.33 (2.10)	6.05 (1.95)
Day 28	4.72 (2.22)	6.94 (2.52)	3.76 (2.46)	4.04 (2.50)	5.38 (1.85)
Day 42	5.04 (2.31)	6.89 (2.53)	3.61 (2.55)	3.42 (2.39)	4.94 (2.01)
Day 56	5.00 (2.39)	6.89 (2.49)	3.33 (2.49)	3.47 (2.48)	4.22 (2.07)
Day 63	5.45 (2.11)	6.63 (2.56)	2.90 (2.73)	3.42 (2.73)	3.94 (1.95)
Day 70	5.50 (2.24)	6.52 (2.71)	2.76 (2.46)	3.33 (2.47)	3.83 (2.09)

Table 7.10. Analysis of variance and simple effects on 'Tense-Relaxed' visual analogue scores at each assessment stage during treatment.

(i) Two factor ANOVA with repeated measures on B

	df	F	p
Factor A (treatment group)	4,96	6.35	0.000***
Factor B (time of assessment)	8,768	68.80	0.000***
Interaction, A X B	32,768	4.81	0.000***

(ii) Simple effects (SS, Factor A)

	df	F	p	Scheffe
Day -7	4,96	0.31	0.864	
Day 0	4,96	1.47	0.214	
Day 7	4,96	2.16	0.079	
Day 14	4,96	4.99	0.0011**	2-3*,2-4**
Day 28	4,96	5.81	0.0003***	2-3**,2-4**
Day 42	4,96	6.77	0.0001***	2-3**,2-4***
Day 56	4,96	7.21	0.0000***	2-5*,2-3***,2-4***
Day 63	4,96	7.88	0.0000***	1-3*,2-5*,2-4**,2-3***
Day 70	4,96	8.54	0.0000***	1-3*,2-5*,2-4**,2-3***

(iii) Simple effects (SS, Factor B)

DZ	8,768	8,14	0.000***
PL	8,768	2.03	0.040*
CBT	8,768	32.03	0.000***
DZ + CBT	8,768	26.58	0.000***
PL + CBT	8,768	20.12	0.000***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Key : Post-hoc Scheffe treatment group comparisons :- 1 = DZ; 2 = PL; 3 = CBT; 4 = DZ + CBT; 5 = PL + CBT

Note : Groups separated by a hyphen differ significantly from each other.

All treatment groups showed a significant within-group shift from 'Tense' to 'Relaxed' anchor points on the visual analogue at the $p < 0.001$ level, apart from the PL group which achieved a significant result at the $p < 0.005$ level. In keeping with HAM-A and SRT results there was no evidence of a shift towards the 'Tense' end of the continuum during graded-withdrawal for the DZ and DZ + CBT groups ($t = 1.18$, $df = 21$, $p = 0.0250$; $t = 0.00$, $df = 20$, $p = 1.000$) or following cessation of all tablet consumption between Days 63 and 70 ($t = 0.37$, $df = 21$, $p = 0.715$; $t = 0.27$, $df = 20$, $p = 0.793$). Comparison of pre (Day -7) and post (Day 70) 'Tense-Relaxed' visual analogue scores revealed a significant reduction for CBT ($t = 9.15$, $df = 20$, $p < 0.001$), DZ + CBT ($t = 6.94$, $df = 20$, $p < 0.001$), PL + CBT ($t = 7.24$, $df = 17$ $p < 0.001$) groups, and to a lesser extent DZ ($t = 3,29$, $df = 21$, $p < 0.005$) and PL ($t = 2.31$, $df = 18$, $p< 0.05$) groups.

e) <u>'Target-Symptom' visual analogue</u>. Table 7.11 presents the 'Target-Symptom' visual analogue means and standard deviations for each treatment group at each assessment stage during treatment. The between-group analysis revealed a significant group ($F (4,96) = 5.20$, $p < 0.005$), time ($F(7,672) = 82.27$, $p < 0.001$) and interaction effect ($F (28,672) = 5.29$, $p < 0.001$) indicating differential changes across groups. At Day 28 significant differences between PL and both CBT and DZ + CBT groups emerged and were maintained throughout the study period. At Day 63 and Day 70, DZ and CBT groups differed. DZ and DZ + CBT groups only differed at Day 70. These results are presented in Table 7.12.

Table 7.11. 'Target-Symptom' visual analogue means and standard deviations (SD) for treatment groups at each assessment stage during treatment.

Target-Symptom Visual analogue	DZ	PL	CBT	DZ+CBT	PL+CBT
Day 0	7.59 (1.70)	7.63 (2.14)	8.09 (1.54)	7.85 (1.38)	8.38 (1.65)
Day 7	5.09 (2.56)	6.57 (2.16)	6.04 (2.39)	5.71 (1.92)	7.11 (2.02)
Day 14	4.59 (2.36)	6.26 (2.64)	4.66 (2.41)	4.52 (1.94)	5.72 (2.39)
Day 28	4.63 (2.46)	6.63 (2.24)	3.52 (2.48)	3.61 (2.15)	5.50 (2.64)
Day 42	4.72 (2.54)	6.47 (2.75)	3.28 (2.43)	2.95 (1.74)	4.11 (1.99)
Day 56	4.72 (2.79)	6.10 (2.76)	2.76 (2.43)	3.09 (1.81)	3.94 (2.53)
Day 63	5.04 (2.64)	5.84 (2.89)	2.42 (2.33)	2.71 (2.05)	3.44 (2.25)
Day 70	5.40 (2.53)	5.84 (2.87)	2.52 (2.62)	2.66 (2.12)	3.72 (2.44)

Table 7.12 Analysis of variance and simple effects on 'Target-Symptom' Visual Analogue scores at each assessment stage during treatment.

(i) Two-factor ANOVA with repeated measures on B.	df	F	p
Factor A (treatment group)	4,96	5.20	0.001**
Factor B (time of assessment)	7,672	82.27	0.000***
Interaction A X B	28,672	5.29	0.000***

(ii) Simple effects (SS, Factor A)

	df	F	p	Scheffe
Day 0	4,96	0.74	0.561	
Day 7	4,96	2.40	0.055	
Day 14	4,96	2.22	0.072	
Day 28	4,96	5.49	0.0005***	2-3**,2-4**
Day 42	4,96	7.11	0.0000***	2-3**,2-4***
Day 56	4,96	5.90	0.0003***	2-3**,2-4**
Day 63	4,96	7.45	0.0000***	1-3*,2-3**,2-4**
Day 70	4,96	7.53	0.0000***	1-3*,1-4*,2-3**,2-4**
(iii) Simple effects (SS, Factor B)				
DZ	7,672	9.44	0.000***	
PL	7,672	2.75	0.008**	
CBT	7,672	36.57	0.000***	
DZ + CBT	7,672	30.47	0.000***	
PL + CBT	7,672	24.69	0.000***	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Key : Post-hoc Scheffe treatment group comparisons :- 1 = DZ; 2 = PL; 3 = CBT; 4 = DZ + CBT; 5 = PL + CBT

Note : Groups separated by a hyphen differ significantly from each other.

All treatment groups showed a significant within-group shift for their individual 'Target-Symptom' from 'extremely bad, could not be worse,' to 'not at all bothered'; at the $p < 0.001$ level, apart from the PL group which achieved a significant result at the $p < 0.01$ level. In parallel with other results there was no evidence of a shift from the 'not at all bothered' end of the continuum during graded-withdrawal for the DZ and DZ + CBT groups ($t = 0.78$, $df = 21$, $p = 0.444$; $t = 0.61$, $df = 20$, $p = 0.548$) or following cessation of all tablet consumption between Day 63 and 70 ($t = 1.40$, $df = 21$, $p = 0.176$; $t = 0.29$, $df = 20$, $p = 0.771$). Comparison of pre (Day 0) and post (Day 70) Target-Symptom visual analogue scores revealed a significant reduction for DZ ($t = 4.45$, $df = 21$, $p < 0.001$), CBT ($t = 9.29$, $df = 20$, $p < 0.001$), DZ + CBT ($t = 9.08$, $df = 20$, $p < 0.001$), PL + CBT ($t = 7.11$, $df = 17$, $p < 0.001$) groups, and to a lesser extent the PL group ($t = 3.54$, $df = 18$, $p < 0.005$).

f) Severity of GAD : The previously mentioned results establish the statistically significant changes in group comparisons over time using specific assessment scales. However it is regarded as important to assess overall clinical ratings of change.

i.) GP Severity Ratings :Table 7.13 presents GPs' assessments of Severity of GAD at study entry (Day -7) and at the end of the study period (Day 70). At Day -7 there was no significant difference in the proportion of patients allocated by referring GPs to the various categories of symptom severity for each of the

Table 7.13. GP ratings of severity of patients' GAD pre-(Day -7) and post-(Day 70) treatment.

Day -7 Symptom Severity	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Normal	-	-	-	-	-
2	-	-	-	-	-
3 - Mild	3(13.6)	1(5.3)	2(9.5)	4(19.0)	2(11.1)
4	4(18.2)	4(21.1)	5(23.8)	3(14.3)	2(22.2)
5 - Moderate	9(40.9)	11(57.9)	9(42.9)	8(38.1)	9(50.0)
6	5(22.7)	3(15.8)	3(14.3)	5(23.8)	3(16.7)
7 - Severe	1(4.5)	-	2(9.5)	1(4.8)	-

(Chi square = 7.45, df = 16, p = 0.963)

Day 70 Symptom Severity	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Normal	1(4.5)	1(5.3)	4(19.0)	10(47.6)	4(22.2)
2	2(9.1)	2(10.5)	7(33.3)	5(23.8)	6(33.3)
3 - Mild	9(40.9)	2(10.5)	6(28.6)	4(19.0)	3(16.7)
4	3(13.6)	5(26.3)	2(9.5)	1(4.8)	3(16.7)
5 - Moderate	4(18.2)	7(36.8)	2(9.5)	1(4.8)	1(5.6)
6	2(9.1)	2(10.5)	-	-	1(5.6)
7 - Severe	1(4.5)	-	-	-	-

(Chi square = 43.59, df= 24, p = 0.008)

treatment groups (χ^2 = 7.45, df = 16, p = 0.963). For each treatment group the largest single severity category on the 1 - 7 scale was '5 - moderate severity;' and the majority of patients fell in the 'moderate' to 'severe' categories. However, at Day 70 the proportion of patients allocated to each category differed between groups (χ^2 = 43.59; df = 24, p < 0.01). The largest single category for each of the treatment groups was as follows; DZ - (mild); PL - (moderate); CBT - (mild/moderate); DZ + CBT - (normal); PL + CBT - (mild/moderate).

ii) Psychologist Severity Ratings : Table 7.14 illustrates the current author's assessment of patients' severity of GAD at Day 0 and Day 70. At Day 0 there was no significant difference between groups in the proportion of patients allocated to the various categories of symptom severity (χ^2 = 16.74, df = 16, p = 0.402). At Day 0, in agreement with the referring GPs, the current author placed a majority of patients in each group in the moderate severity category. At Day 70 the proportion of patients allocated by the current author to each category differed between treatment groups (χ^2 = 41.84, df = 24, p <0.05).

Although the referring GPs and the current author carried out independent assessments of patient severity without prior collaboration there was nevertheless a satisfactory level of agreement at Day 0 (Pearson r = 0.41, p < 0.001) and especially at Day 70 (Pearson r = 0.854, p <0.001).

Table 7.14. Psychologist ratings of severity of patients' GAD pre-(Day -7) and post-(Day 70) treatment.

Day -7 Symptom Severity	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Normal	-	-	-	-	-
2	-	-	-	-	-
3 - Mild	-	-	-	1(4.8)	-
4	1(4.5)	-	3(14.3)	-	-
5 - Moderate	15(68.2)	15(78.9)	12(57.1)	12(57.1)	15(83.3)
6	5(22.7)	4(21.1)	5(23.8)	6(28.6)	2(11.1)
7 - Severe	1(4.5)	-	1(4.8)	2(9.5)	1(5.6)

(Chi square = 16.74, df = 16, p = 0.402)

Day 70 Symptom Severity	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Normal	1(4.5)	1(5.3)	3(14.3)	6(28.6)	2(11.1)
2	4(18.2)	1(5.3)	11(52.4)	10(47.6)	5(27.8)
3 - Mild	3(13.6)	4(21.1)	2(9.5)	3(14.3)	4(22.2)
4	6(27.3)	3(15.8)	1(4.8)	1(4.8)	3(16.7)
5 - Moderate	6(27.3)	7(36.8)	4(19.0)	1(4.8)	3(16.7)
6	2(9.1)	3(15.8)	-	-	-
7 - Severe	-	-	-	-	1(5.6)

(Chi square = 41.84, df= 24, p = 0.013)41.84, df = 24, p < 0.05).

g) Overall Symptom Change : Overall symptom change at Day 70, from Day -7 (for GPs) and Day 0 (for the current author), are presented in Tables 7.15 and 7.16 respectively. Table 7.17 shows patients' self-assessment of their overall symptom change from Day -7 to Day 70. All assessors indicated that overall symptom change at Day 70 differed between treatment groups; GPs (χ^2 = 53.32, df = 16, $p < 0.001$); the current author (χ^2 = 38.47, df = 16, $p < 0.005$); patients' self-rating (χ^2 = 36.66, df = 20, $p < 0.05$).

Arbitrarily taking the categories of 'very much improved' and 'much improved' as indicative of significant clinical improvement, GPs regarded 45% of DZ; 36% of PL; 86% of CBT; 87% of DZ + CBT and 72% of PL + CBT groups as achieving this status (Table 7.15). In general, similarly proportioned representations of significant clinical improvement were noted by the current author and by patients own self-report (Tables 7.16 and 7.17). High levels of agreement regarding overall symptom change existed between GP and psychologist (Pearson r = 0.93, $p < 0.001$), GP and patient (Pearson r = 0.89, $p < 0.001$), and psychologist and patient (Pearson r = 0.94, $p < 0.001$).

Table 7.15. GP Ratings of overall symptom change post-treatment (Day 70).

Day 70 Symptom Change	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Very much improved	4(18.2)	3(15.8)	14(66.7)	16(76.2)	9(50.0)
2 - Much improved	6(27.3)	2(10.5)	4(19.0)	2(9.5)	4(22.2)
3 - Minimally improved	8(36.4)	2(10.5)	1(4.8)	3(14.3)	2(11.1)
4 - No change	3(13.6)	12(63.2)	2(9.5)	-	2(11.1)
5 - Minimally worse	1(4.5)	-	-	-	1(5.6)
6 - Much worse	-	-	-	-	-
7 - Very much worse	-	-	-	-	-

(Chi square = 53.32, df = 16, p = 0.000)

Table 7.16. Psychologist Ratings of overall symptom change post-treatment (Day 70).

Day 70 Symptom Change	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Very much improved	7(31.8)	3(15.8)	16(76.2)	16(76.2)	9(50.0)
2 - Much improved	5(22.7)	3(15.8)	2(9.5)	3(14.3)	5(27.8)
3 - Minimally improved	6(27.3)	4(21.1)	2(9.5)	2(9.5)	1(5.6)
4 - No change	2(9.1)	8(42.1)	1(4.8)	-	2(11.1)
5 - Minimally worse	2(9.1)	1(5.3)	-	-	1(5.6)
6 - Much worse	-	-	-	-	-
7 - Very much worse	-	-	-	-	-

(Chi square = 53.32, df = 16, p = 0.0013)

Table 7.17. Patients' self-rating of overall symptom change post-treatment (Day 70).

Day 70 Symptom Change	DZ n(%)	PL n(%)	CBT n(%)	DZ+CBT n(%)	PL+CBT n(%)
1 - Very much improved	6(27.3)	4(21.1)	16(76.2)	15(71.4)	11(61.1)
2 - Much improved	5(22.7)	3(15.8)	3(14.3)	2(9.5)	2(11.1)
3 - Minimally improved	4(18.2)	2(10.5)	1(4.8)	4(19.0)	2(11.1)
4 - No change	5(22.7)	8(42.1)	1(4.8)	-	2(11.1)
5 - Minimally worse	2(9.1)	1(5.3)	-	-	-
6 - Much worse	-	1(5.3)	-	-	1(5.6)
7 - Very much worse	-	-	-	-	-

(Chi square = 36.66, df = 20, p = 0.0128)

h) Treatment Outcome: Jacobson et al (1984) highlighted the inadequacies of treatment efficacy results which were based solely on statistical comparisons between two or more treatment conditions. They noted that such comparisons have two conventional properties which limit their usefulness in outcome research. Firstly, "that they are based on the average improvement score for all subjects and thus provide no information on the effects of therapy for individual clients". Secondly "that the 'significance test' itself imposes a criterion for determining a treatment effect which often has little clinical relevance".

While the above presentation of Severity Ratings and Overall Symptom Change assessments may partially accommodate such criticisms, Jacobson et al (1984) recommended a number of formulae for computing clinically significant change. Lindsay et al (1987) stated that the most stringent of these is to assess whether a patient's outcome response falls outside the range of the dysfunctional population by two standard deviations from the pretreatment mean of that population, in the direction of functionality. Table 7.18 illustrates the number of patients achieving this criterion at Day 70 on the HAM-A, SRT, GHQ, 'Tense-Relaxed' visual analogue, and 'Target-Symptom visual analogue.

On all the measures the DZ + CBT group consistently has the largest percentage of patients showing 'clinically significant change'. The CBT group shows a similarly consistent pattern of improvement, although the magnitude of the effect is less pronounced.

Table 7.18. Number and (%) of patients in each group who do, or do not, achieve 'Clinically Significant Change', at Day 70.

	'Clinically Significant Change'									
	DZ		PL		CBT		DZ+CBT		PL+CBT	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
HAM-A	15 (68.2)	7 (31.8)	7 (36.8)	12 (63.2)	18 (85.7)	3 (14.3)	19 (90.5)	2 (9.5)	15 (83.3)	3 (16.7)
SRT	7 (31.8)	15 (68.2)	5 (26.3)	14 (73.7)	16 (76.2)	5 (23.8)	18 (85.7)	3 (14.3)	9 (50.0)	9 (50.0)
GHQ	7 (31.8)	15 (68.2)	5 (26.3)	14 (73.7)	15 (71.4)	6 (28.6)	19 (90.5)	2 (9.5)	13 (72.2)	5 (27.8)
'Tense-relaxed'	8 (36.4)	14 (63.6)	3 (15.8)	16 (84.2)	16 (76.2)	5 (23.8)	15 (71.4)	6 (28.6)	11 (61.1)	7 (38.9)
'Target symptom'	8 (36.4)	14 (63.6)	6 (31.6)	13 (68.4)	16 (76.2)	5 (23.8)	17 (81.0)	4 (19.0)	13 (72.2)	5 (27.8)

With the exception of SRT results the PL + CBT group also reveal a similar pattern of the majority of patients reporting 'clinically significant change', although to a lesser extent than the CBT and DZ + CBT groups. With the exception of the HAM-A results, the majority of the DZ patients failed to achieve 'clinically significant change'. The PL group consistently showed the lowest number of patients achieving 'clinically significant change' on all anxiety measures.

i) Follow-Up: As mentioned in the Pilot Study, adequate follow-up data are often difficult to collect and evaluate as patients may require subsequent treatment between the end of the study period and the designated follow-up date. To circumvent this difficulty collation of 'unobtrusive measures' at follow-up has been recommended by Bellack and Hersen (1984). Table 7.19 illustrates the number of patients in each group who received psychological or psychiatric referral, or psychotropic medication during the 6 months period post-study. The number of patients who received subsequent treatment differed between groups (X^2 = 17.96, df = 4, $p < 0.005$). The majority of DZ and PL patients received subsequent treatment, while most of the CBT, DZ + CBT, and PL + CBT patients did not.

Analysis of the numbers of patients who received psychotropic medication in the six months post-study period revealed no significant difference between groups (X^2 = 8.57, df = 4, p = 0.072) as illustrated in Table 7.20.

However there was a significant difference between groups in

Table 7.19 . Number and (%) of patients receiving psychological, or psychiatric referral, or psychotropic medication during 6 month period post-study.

Subsequent Treatment	DZ	PL	CBT	DZ+CBT	PL+CBT
Yes	12 (57.1)	12 (70.6)	4 (21.1)	3 (15.8)	5 (27.8)
No	9 (42.9)	5 (29.4)	15 (78.9)	16 (84.2)	13 (72.2)

(Chi square = 17.96, df = 4, p = 0.0013)

Table 7.20 . Number and (%) of patients prescribed psychotropic medication during 6 month period post-study.

Psychotropics	DZ	PL	CBT	DZ+CBT	PL+CBT
Yes	7 (33.3)	9 (52.9)	3 (15.8)	2 (10.5)	5 (27.8)
No	14 (66.7)	8 (47.1)	16 (84.2)	17 (89.5)	13 (72.2)

(Chi square = 8.57, df = 4, p = 0.072)

Table 7.21. Number and (%) of patients receiving psychological or psychiatric referral during 6 month period post-study.

Psychological/ Psychiatric referral	DZ	PL	CBT	DZ+CBT	PL+CBT
Yes	12 (57.1)	6 (35.3)	2 (10.5)	3 (15.8)	1 (5.6)
No	9 (42.9)	11 (64.7)	17 (89.5)	16 (84.2)	17 (94.4)

(Chi square = 19.08, df = 4, p = 0.0008)

the number of patients who received psychological or psychiatric referrals from their GP in the 6 months post-study period (X^2 = 19.08, df = 4, p < 0.001). Table 7.21 shows that the overwhelming majority of CBT, DZ + CBT, and PL + CBT patients received no such referrals. A minority of PL patients received subsequent referrals. Only in the DZ Group were the majority of patients referred for psychological or psychiatric treatment during the 6 months post-study period.

All patients were asked to attend for a six-month follow-up appointment. Table 7.22 illustrates that, with the exception of the PL group, the vast majority of all patients attended for this follow-up assessment. Of the 3 non-attenders from the DZ group, 1 had changed both address and GP and was therefore untraceable, the remaining 2 simply failed to attend without providing explanation. The 2 CBT non-attenders had also changed both address and GP and therefore could not be contacted. Two CBT + DZ patients had also moved house and changed GP, and a further 2 simply failed to attend. For the PL + CBT group 2 patients also failed to appear for follow-up assessment. However from the PL group only 8 of 19 patients attended for follow-up. Of the remaining 11 non-attender PL patients; 1 had died, 1 had emigrated, 1 had moved house and changed GP, and 8 failed to attend without explanation.

Given the confounding influence of post-study treatment on status at follow-up the results in Table 7.22 are only for attenders at follow-up who had received no psychotropic,

Table 7.22. Number and (%) of patients with no subsequent post-study treatment who achieve 'clinically significant change' at 6 month follow-up assessment.

	DZ	PL	CBT	DZ+CBT	PL+CBT
	n = 22	n = 19	n = 21	n = 21	n = 18
	n(%)	n(%)	n(%)	n(%)	n(%)
No of follow-up attenders	19 (86.4)	8 (42.1)	19 (90.5)	17 (81.0)	16 (88.9)
No of follow-up attenders with no subsequent treatment	9 (40.9)	5 (26.3)	15 (71.4)	16 (76.2)	13 (72.2)
No of follow-up attenders with no subsequent treatment who achieve 'clinically significant change' on :-					
HAM-A	9 (40.9)	4 (21.0)	15 (71.4)	15 (71.4)	12 (66.7)
SRT	5 (22.7)	3 (15.8)	11 (52.4)	14 (66.7)	9 (50.0)
GHQ	6 (27.3)	3 (15.8)	13 (61.9)	15 (71.4)	9 (50.0)
'Tense-relaxed'	5 (22.7)	3 (15.8)	14 (66.7)	14 (66.7)	9 (50.0)
'Target Symptom'	8 (36.4)	3 (15.8)	15 (71.4)	14 (66.7)	8 (44.4)

psychological or psychiatric subsequent treatment.

The majority of CBT, DZ + CBT, and PL + CBT attenders had not received treatment post study. However only a minority of the DZ, and PL attenders had received no treatment post-study. At six months follow-up assessment the DZ + CBT, and CBT group had maintained initial treatment gains. This is evident by the majority of patients in both groups showing 'clinically significant change' on the anxiety measures without recourse to any subsequent post-study treatment. At Day 70 the PL + CBT groups had shown the third greatest reduction in anxiety, this relative rank was also seen at follow-up when approximately 50% of PL + CBT patients exhibited 'clinically significant change'. The DZ group had the second lowest number of patients achieving clinically significant change at follow-up. The PL group contained the lowest number of patients achieving clinically significant change at follow-up. However in this PL group only 42% of patients attended for follow-up, whereas all other groups achieved at least an 80% attendance rate. The 8 patients from the PL group who simply failed,without explanation,to attend for follow-up were characterised by poor response to treatment. In particular, at Day 70, these 8 PL patients all failed to achieve 'clinically significant change' status on the HAM-A, and only 1 of the 8 patients achieved such status on the SRT. For these 8 patients comparison of Day 0 and Day 70 on the HAM-A, and Day -7 and Day 70 on the SRT failed to produce any significant reduction in symptoms ($t = 1.57$, $df = 7$, n.s. ; $t = 1.38$, $df = 7$, n.s.). So they were a group which failed

to respond to treatment, and this lack of therapeutic impact may have made them reluctant to attend for follow-up.

DISCUSSION

At Day 70 all treatment groups had improved to a greater or lesser extent on the HAM-A, SRT, Tense-Relaxed and Target-Symptom measures. All groups apart from PL showed significant GHQ reductions.

Differences between groups in the rate of symptom reduction first emerged at Day 14 on the Tense-Relaxed visual analogue, followed at Day 28 by the HAM-A and the Target-Symptom visual analogue. Between-group differences on the SRT did not emerge until Day 42. On the above measures these early differences favoured DZ + CBT and/or CBT over PL. Differences in favour of DZ + CBT in comparison to DZ emerged at a similar stage on the HAM-A and SRT but at a later stage on the Target Symptom measure. Differences in favour of CBT in comparison to DZ eventually occurred on the HAM-A, Tense-Relaxed, and Target-Symptom measures. The HAM-A and Tense-Relaxed measures also showed differences in favour of PL + CBT in comparison to PL. At Day 70 the GHQ showed differences in favour of DZ + CBT, and CBT in comparison to PL and DZ. At no point did CBT, DZ + CBT, and PL + CBT groups differ. Similarly at no point did DZ and PL groups differ. Few between-group differences emerged in the first two weeks of the study, all groups seemed to be improving at a similar rate. However, at

approximately Day 14 to Day 28, PL and DZ treatment gains began to plateau, while CBT, DZ + CBT, and PL + CBT continueed to improve.

The present study permits comparison of statistically significant change on specific anxiety measures vs. clinically rated change as assessed by psychologist and GP severity ratings; psychologist, GP, and patient self-reports of overall symptom change; and Jacobson et al's (1984) formulae for 'clinically significant change'.

The PL group produced small but statistically significant reductions on most of the anxiety measures during treatment. However the clinical significance of these changes for the PL group was far less impressive, and 70% of patients required subsequent treatment in the 6 months post-study period. It is not surprising that few PL patients attended for follow-up if they regarded the treatment they received in the study as lacking efficacy.

As a group the DZ patients appeared to respond well if one looks at pre and post-study statistically significant reductions on the specific anxiety measures. However, at Day 70, only a minority of the DZ patients achieved 'clinically significant change' on the anxiety measures, except the HAM-A where a majority of DZ patients did achieve such status. Although the majority of DZ patients were rated as 'minimally' or 'much' improved by the current author, GP, and self-report at Day 70, this treatment gain was not of adequate magnitude or permanence to prevent 57% of them requiring subsequent treatment in the 6 months post-study period.

CBT, DZ + CBT, and PL + CBT groups all achieved pre and post-study statistically significant reductions on the specific anxiety measures. In addition at Day 70 both referring GP and the current author rated a larger percentage of the CBT, DZ + CBT and PL + CBT groups as veering towards an absence of symptoms, on the severity rating, in comparison to DZ and PL groups. This trend was also reflected by the majority of CBT, and DZ + CBT patients being rated as 'very much improved' by GPs, the current author and patients self-report. After treatment on Day 70 the DZ + CBT in particular, followed by the CBT group consistently produced the largest percentage of patients achieving 'clinically significant change'. Follow-up revealed a low rate of subsequent treatment and a high rate of maintained improvement for the DZ + CBT and CBT groups. Although the PL + CBT group did not differ from CBT and DZ + CBT groups on statistical analysis of the specific anxiety measures during treatment, there was a tendency for the magnitude of PL + CBT symptom reduction to be less impressive. This pattern of results was reinforced at Day 70, with only 50% of the PL + CBT group rated by GP, and the current author as 'very much improved'. Similarly, smaller percentages of the PL + CBT group achieved 'clinically significant change', at Day 70 on the SRT and 'Tense-Relaxed' measures in comparison to CBT and DZ + CBT groups. At follow-up slightly fewer PL + CBT patients maintained 'clinically significant change' on the HAM-A in comparison to CBT and DZ + CBT groups. Similarly at follow-up only 50% of the PL + CBT achieved 'clinically significant change' on the SRT, GHQ and Tense-Relaxed

measures. Overall, the degree of 'clinically significant change' achieved by the PL + CBT tended to be less than that attained by the CBT and DZ + CBT groups. However this did not lead to any major differences in the number of PL + CBT patients receiving post-study treatment in comparison to CBT and DZ + CBT groups.

The effect that benzodiazepines may have on the efficacy of psychological treatment was discussed in Chapter 4. It has been argued that concurrent benzodiazepine use may diminish or enhance the effectiveness of psychological treatment (Miller 1986). Furthermore, withdrawal of concurrent benzodiazepines may lead to relapse if patients attribute clinical improvement to the anxiolytic effect of medication (Sartory 1983). These points are relevant to the present research. In particular, if patients in the DZ group attributed treatment gains solely to the drug, then discontinuation of the medication may indeed lead to relapse. This phenomenon may explain the high rate of subsequent treatment received by the DZ group, and even those in the PL group, who had responded positively during treatment. However, this does not appear to apply to the DZ + CBT group which, although not significantly different from the CBT and PL + CBT groups, exhibited the greatest reductions on specific anxiety measures, and attained the highest percentage of patients achieving 'clinically significant change' at Day 70 and at follow-up. Diazepam in combination with cognitive-behaviour therapy did not appear to impede psychological treatment or lead to relapse in DZ + CBT patients. Rather diazepam may have had a beneficial impact on

treatment outcome and follow-up in the DZ + CBT group. This may be responsible for the DZ + CBT group consistently being one of the first groups to show early treatment gains compared to PL controls. The less impressive results of PL + CBT in comparison to CBT and DZ + CBT may be explained by patient expectations regarding the benefit of placebo medication not being met. Patients in the PL + CBT group may thus have expected the placebo medication to partially ameliorate their anxiety state, (as diazepam may have done for the DZ + CBT group). Therefore PL + CBT patients may have applied cognitive-behaviour therapy techniques with less vigour and greater passivity than those in the CBT alone group. The unfulfilled expectation of placebo efficacy, coupled with diminished levels of cognitive behaviour therapy application, may have impaired the effectiveness of PL + CBT treatment and reduced the percentage of patients achieving clinically significant change at Day 70, and follow-up.

Anxiety reduction in the CBT group was second to that in the DZ + CBT group but these groups were not significantly different. The present study therefore shows that CBT is a viable method of anxiety management which has lasting results at follow-up.

Although the PL and to a lesser extent the DZ groups failed to attain and maintain the levels of anxiety reduction achieved by the CBT, DZ + CBT, and PL + CBT groups, it is nevertheless important to note that a small but significant proportion of DZ patients did achieve 'clinically significant change' status at Day 70, and thereafter at follow-up without subsequent post study

treatment. In the Pilot Study (Chapter 6) 70% of diazepam patients required some form of treatment in the 12-month period post-study. In the present study, albeit only a 6-month follow-up, only 57% of DZ patients required subsequent treatment. The reduction in the number of DZ patients requiring post-study treatment in the present study, in comparison to the Pilot Study, may be due to the implementation of a graded-withdrawal programme for both the DZ and DZ + CBT groups. Neither DZ nor DZ + CBT patients showed any significant elevations of HAM-A, SRT, Tense-Relaxed, and Target-Symptom measures during graded-withdrawal. As previously mentioned in the Pilot Study, Owen and Tyrer (1983) suggested that a temporary increase in pre-existing symptoms and the presentation of new symptoms may indicate a withdrawal syndrome. The Main Study did not reveal an increase in pre-existing symptoms for the DZ and DZ + CBT groups during graded-withdrawal, neither were major withdrawal symptoms experienced. A few patients from the DZ, and DZ + CBT groups complained of mild agitation, an increase in the vividness of dreams, and some disturbed sleep, during and immediately following graded-withdrawal. However these symptoms were mild and of no major concern to the patients. The Pilot Study suggested that a reappraisal of the use of benzodiazepines was necessary and advocated graded-withdrawal. The present study suggests that although diazepam appears less effective than cognitive-behaviour therapy for the management of GAD, the pharmacological approach should not be discarded completely. As a first line of treatment diazepam produces clinically significant

results for a substantial minority of patients. Although these results are not wholly maintained at follow-up the introduction of a placebo substitution graded-withdrawal programme, after a relatively short course of treatment, maximizes initial gains and limits withdrawal symptoms, thereby possibly reducing subsequent dependence.

A number of criticisms pertaining to the Pilot Study also apply to the Main Study. There was no formal assessment of CBT or skill of the current author as sole therapist. Unfortunately this was beyond the scope of the present study. Although CBT was administered according to structured guidelines presented in section 6.2.2, the particular emphasis placed on the amelioration of cognitive, behavioural, and somatic components varied according to patients' specific presenting problems. The superiority of CBT whether alone or in combination cannot be attributed solely to the amount of psychologist attention patients received. DZ and PL groups received a similar amount of attention during which the current author conducted enquiries about response to treatment in a non-directive manner so as to avoid making suggestions of a therapeutic nature. Thus, certain components of cognitive-behaviour therapy, apart from the amount of non-directive counselling the patient receives, are likely to be responsible for treatment gains and maintained improvement at follow-up. At present one can only speculate as to which components of cognitive-behaviour therapy are important. However from a patient's viewpoint the fact that they themselves feel that they can control

their symptoms and that their worst fears will not be realized may enhance long-term treatment gains. Cognitive-behaviour therapy also teaches patients that they are responsible for treatment gains and alleviates their central fear that they will 'lose control' in some manner or other. Cognitive-behaviour therapy is a more active and directive form of anxiety management, than the more passive form of long-term benzodiazepine use.

In summary, the present study suggests that short-term diazepam with graded-withdrawal is still a treatment strategy worth pursuing given the substantial minority of patients who respond positively to it, and the often long waiting-list for psychological treatment. However treatment gains with diazepam are not always well maintained. Alternatively cognitive-behaviour therapy produces long standing anxiety reduction for the majority of the patients. Diazepam in conjunction with cognitive-behaviour therapy results in early treatment gains and this combined treatment may be most appropriate for patients suffering from severe GAD. Additionally the current study also suggests that benzodiazepines if used judiciously need not lead to a withdrawal syndrome and subsequent dependence. Given the growing demands from the lay press and the current recommendations of the Committee for Safety of Medicines that patients be withdrawn from long-term benzodiazepine use, the characteristics of a long-term user population will be investigated in the next chapter.

CHAPTER 8 : SECONDARY STUDY

8.1.1 A controlled comparison of characteristics of long-term benzodiazepine users in general practice.

As mentioned in the introductory chapters, long-term use of benzodiazepines is no longer recommended (Committee on the Review of Medicines 1980). The popularity of these drugs (Tyrer 1974; Lader 1978), and subsequent problems of dependency and withdrawal (Murphy et al; Power et al 1985) have led to various estimates of the number of patients on long-term repeat prescription (Balter et al 1984; Mellinger et al 1984). Growing concern about the number of patients on long-term benzodiazepine maintenance has been reflected both in medical journals (Drury 1985; Tyrer and Murphy 1987) and the lay press (Cohen 1983).

Although numerous articles have been published concerning the characteristics of heterogeneous groups of psychotropic drug users (Parish 1971; Skegg et al 1977; Cooperstock 1978; Murray et al 1981), there is a paucity of papers, especially in the United Kingdom, concerned with benzodiazepine users in particular. Of two recently published papers, concerned with characteristics of long-term benzodiazepine users (Salinsky and Dore 1987; Rodrigo et al 1988), only one (Salinsky and Dore 1987) incorporated a matched age and sex control group. Both studies were carried out in single general practices and each had a sample size of approximately 70 subjects. These factors compromise the general

applicability of the results. In one of these studies, patients on either benzodiazepine anxiolytics or hypnotics were apparently included (Rodrigo et al 1988), while in the other study patients on an anxiolytic alone, or an anxiolytic plus hypnotic were included (Salinsky and Dore 1987). However neither study assessed the similarities or differences between anxiolytic and/or hypnotic users.

Studies of hypnotic users have often included non-benzodiazepine hypnotic drugs (Morgan et al 1988), been limited to the elderly (Morgan 1983), or to those in hospital or residential care settings (Cook et al 1983). Little is known of benzodiazepine hypnotic users in the community.

The current study reports on the characteristics of a large group of long-term benzodiazepine anxiolytic and hypnotic users from three general practices in comparison with matched age and sex controls. As previously noted, the boundary between a benzodiazepine anxiolytic and hypnotic is not absolute in pharmacological terms (Committee on the Review of Medicines 1980) or with regard to how the drug is administered. Nevertheless in the present study it was also decided to investigate differences in those receiving prescriptions for hypnotics alone, anxiolytics alone, and anxiolytics plus hypnotics, as this has not previously been addressed in the literature.

8.1.2 Subjects

The study was conducted, with the consent of the eleven

principal GPs, in three practices of the Forth Valley GP Research Group during December 1987 - February 1988. The three practices comprised approximately 17,000 patients from three main and two branch surgeries in suburban and village environments surrounding Stirling town. One was a dispensing practice. Two were training practices at the time of the study, and the third had just been approved for training. The record systems were A4 with summary sheets which included prescription summaries. All three practices had computerised repeat prescription using the Scottish G-Pass system which enabled an accurate and readily-available list of patients receiving repeat prescription benzodiazepines to be examined.

A total of 445 patients, currently prescribed benzodiazepines, were identified in the three study practices as having received 3 or more consecutive prescriptions of one or more benzodiazepines.

8.1.3 Procedure

A random sub-sample of 205 patients was selected and matched from the age sex register with controls. Two non-medical research assistants ECS and MHB were trained by the present author to conduct a initial review of all patients' case notes. The data collected from case notes were subsequently checked by a principal in general practice (RJS) who was not working in any of the three practices being studied.

8.1.4 Measures

The characteristics of the benzodiazepine group which were noted included age and sex distribution, number of years on benzodiazepines, age at first prescription and current benzodiazepine medication.

Information was also collected for both benzodiazepine users and matched controls on the frequency of consultations and all prescribed medication over the past 10 years where the prescription had been repeated more than once. In addition an analysis was prepared, for both groups, of illnesses in each body system. Any illness recorded on the medical summary or which required specialist referral, or repeat prescription was included. Illness was graded into major and minor episodes (excluding trivial illnesses) and was done blind (between users and controls) by the principal in general practice (RJS).

8.1.5 Results

8.1.5.1 Extent of Use:

The rate for three or more repeat presriptions in the three study practices (17,000 patients) was 26 per 1000 or 2.6%. If extrapolated this would provide an estimate of 133,120 on long-term benzodiazepine medication in Scotland. Whilst no national rate of benzodiazepine prescribing for Scotland is available, the Common Services Agency (Information and Statistics Division) reported 1.78 million hypnotic prescriptions and 1.39 million sedative and

tranquillizer prescriptions as having been issued in 1986 to a Scottish population of 5.123 million.

Table 8.1, adapted from Rodrigo et al (1988), shows the results of some other recent studies that estimated the extent of long-term general 'tranquillizer use' or benzodiazepine use. The results are not directly comparable, in that different groups of drugs are compared between studies. Furthermore other studies have assessed the extent of drug use for more than one year, whereas the present study assessed the frequency of three or more consecutive repeat prescriptions. However 92% of the present study population had received repeat prescriptions for more than one year. Notwithstanding these issues the various estimates provide a valuable insight into the extent of regular benzodiazepine use.

8.1.5.2 Benzodiazepine Patient Characteristics.

The benzodiazepine group comprised 48 (23%) males and 157 (77%) females. The mean age of the benzodiazepine group was 64 years (S.D. = 14 years, range = 27 - 90 years). The mean male age was 59 years (S.D. = 15 years, range 29 - 90 years). The mean female age was 65 years (S.D. = 13 years, range 27 - 88 years). Table 8.2 shows that only a minority (approximately 18%) were currently aged 49 years or below and that the majority of patients (66%) first received a benzodiazepine prescription while aged between 40 and 69 years. These results are illustrated graphically in Figures 5 and 6.

Table 8.1. Estimated extent of long-term use of 'tranquillizers' or benzodiazepines in recent studies.

Stroll and Lader 1984 Community Survey	"Use of tranquillizers for one year or more"	1.5% of men
Mellinger and Balter 1981 Community Survey USA	"Use of anti-anxiety agents for 12 months or more"	1.6% of population
Balter et al 1984 Community Survey Several Countries	"Regular daily use of anti-anxiety/ sedative drugs for 12 months or more"	UK : 3.1% of population USA : 1.8% of population Europe : 1.6% of population
Salinsky and Dore 1987 General Practice, England	"Taking benzodiazepines regularly during the day for more than one year"	1.6 % of registered patients
Rodrigo et al 1988 General Practice, England	"Prescription for benzodiazepines for one year or more"	2.2% of registered patients
Present Study General Practice, Scotland	"Three or more consecutive benzodiazepine prescriptions"	2.6% of registered patients

Table 8.2. Illustrating current age distribution of BZ users and distribution of age at which first prescribed BZs.

Age (Years)	Age Distribution of BZ Users No (%)	Distribution of age at which first prescribed BZs No (%)
20 - 29	2 (1)	11 (5.5)
30 - 39	9 (4.5)	31 (15)
40 - 49	24 (12)	38 (19)
50 - 59	32 (15)	64 (31)
60 - 69	61 (30)	33 (16)
70 - 79	54 (26)	25 (12)
80 - 89	22 (11)	2 (1)
90 - 99	1 (0.5)	1 (0.5)

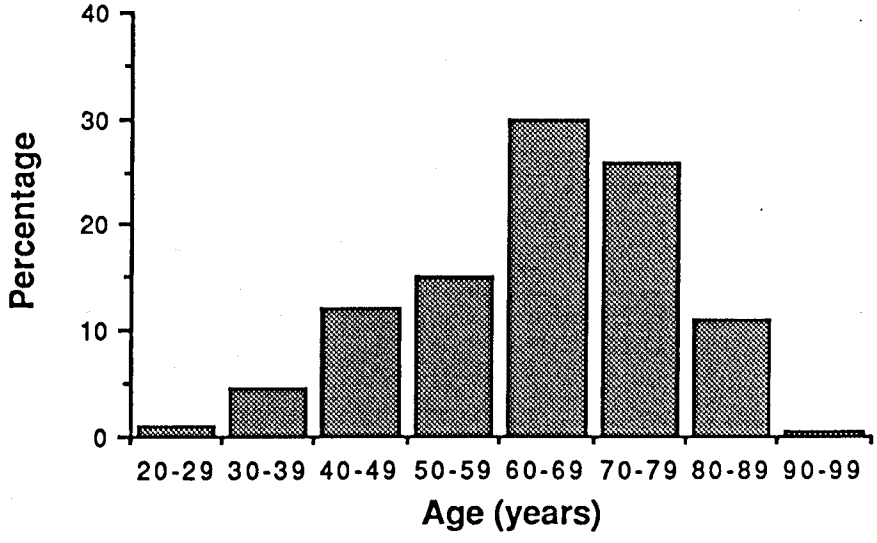

Fig.5. Percentage age distribution of benzodiazepine users (N = 205; 26 per 1000; 2.6% practice pop.)

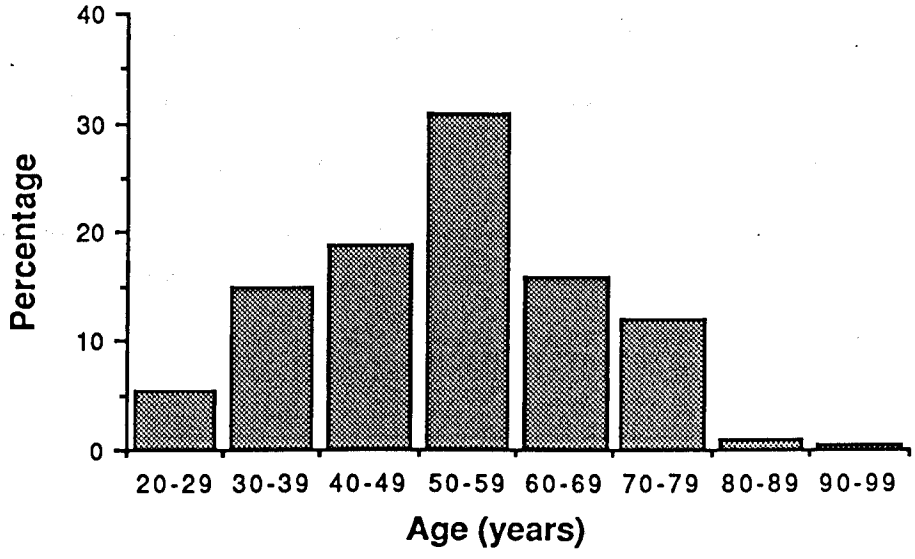

Fig.6. Percentage distribution of age at which first prescribed benzodiazepines (N = 205; 26 per 1000; 2.6% practice pop.)

The mean length of time on repeat prescription benzodiazepines was approximately 8 years (S.D. = 6 years, range = 1 month - 23 years). Table 8.3 shows that of the 201 benzodiazepine users for whom the length of time on repeat prescription could be ascertained, over half (58%) had been in receipt of benzodiazepines for more than 6 years. These results are illustrated graphically in Figure 7.

Table 8.3 Distribution of length of time on repeat prescription BZs

Time (years)	No (%) of BZ users
0 - 1	16 (8)
1 - 5	68 (34)
6 - 10	57 (28)
11 - 15	22 (11)
16 - 20	32 (16)
21 - 25	6 (3)
TOTAL	201 (100)

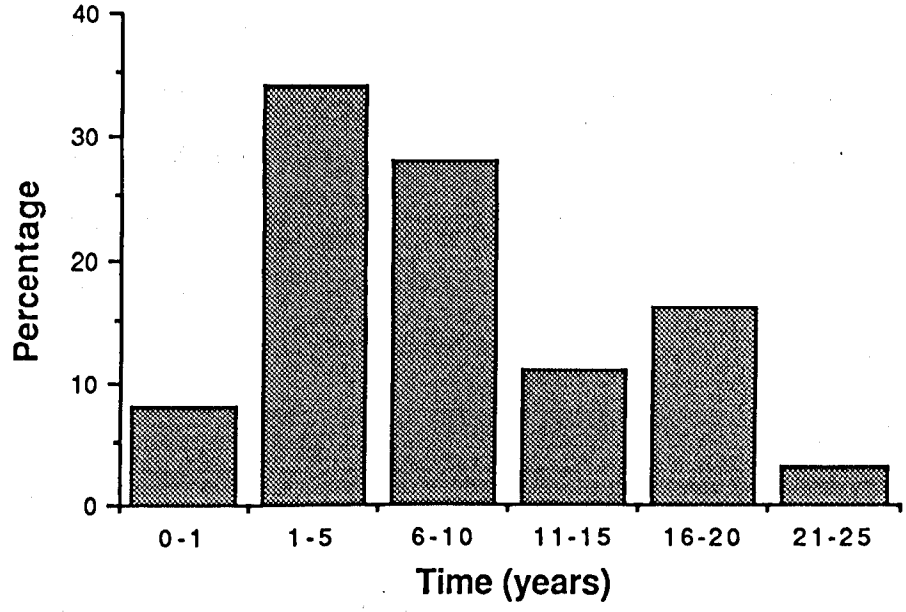

Fig.7. Percentage distribution of length of time on repeat prescription benzodiazepines (N = 201)

8.1.5.3 Benzodiazepine Patients vs. Controls :

Systemic Illness History

Table 8.4 shows that only 18% of benzodiazepine users in comparison to 37% of controls had no history of major systemic illness. Forty per cent of benzodiazepine users had a history of three or more systemic illnesses in comparison to 24% of controls. A similar trend was evident with regard to minor systemic illness, although to a lesser extent, with 15% of benzodiazepine users in comparison to 24% of controls with no recorded minor systemic illness.

Although the differences between the groups are less clear when major and minor systemic illnesses are combined, nevertheless 48% of the benzodiazepine group in comparison with 34% of the control group suffered seven or more major plus minor recorded illnesses.

Table 8.5 illustrates the frequency of previous episodes of major and minor illness in specific systems in benzodiazepine patients and controls. Benzodiazepine patients exhibited significantly more episodes of major cardiovascular illness ($t = 3.81$, $df = 408$, $p < 0.001$), major and minor gastro-intestinal illness ($t = 3.02$, $df = 408$, $p < 0.005$; $t = 3.55$, $df = 408$, $p < 0.001$), major and minor genito-urinary illness ($t = 2.65$, $df = 408$, $p < 0.01$; $t = 2.14$, $df = 408$, $p < 0.05$), major respiratory illness ($t = 3.50$, $df = 408$, $p < 0.01$), major central nervous system illness ($t = 2.17$, $df = 408$, $p < 0.05$) and minor ear nose and throat illness ($t = 2.08$, $df = 408$, $p < 0.05$).

Table 8.4 - Distribution of number of previous major, minor, and major + minor systemic illnesses in benzodiazepine (BZ) users and controls from GP records.

	Major Systemic Illness		Minor Systemic Illness		Major + Minor Systemic Illness	
Number of Recorded Illnesses	No(%) of BZ Users	No(%) of controls	No(%) of BZ Users	No(%) of controls	No(%) of BZ Users	No(%) of Controls
None	36 (18)	76 (37)	31 (15)	49 (24)	7 (13)	24 (12)
1 - 2	85 (42)	79 (39)	81 (40)	87 (42)	42 (21)	62 (30)
3 - 4	56 (27)	40 (19)	46 (22)	44 (22)	57 (28)	52 (25)
5 - 6	15 (7)	8 (4)	21 (10)	11 (5)	33 (16)	35 (17)
7 - 8	11 (5)	2 (1)	16 (8)	8 (4)	25 (12)	16 (8)
9 - 10	2 (1)	-	6 (3)	6 (3)	20 (10)	6 (3)
11 - 12	-	-	4 (2)	-	7 (3)	9 (4.5)
13 +	-	-	-	-	14 (7)	1 (0.5)
TOTAL	205 (100)	205 (100)	205 (100)	205 (100)	205 (100)	205 (100)

Table 8.5. Total number of previous specific episodes of major and minor systemic illnesses in benzodiazepine (BZ) users and control groups from GP records.

	Minor Systemic Illness		Major Systemic Illness	
Nature of Illness	No (%) of BZ Users	No (%) of Controls	No (%) of BZ Users	No (%) of Controls
Cardiovascular	55 (9)	47 (10)	145 (29)	68 (23)
Gastrointestinal	102 (17)	50 (11)	88 (18)	46 (15)
Genitourinary	104 (17)	70 (16)	70 (14)	41 (14)
Respiratory	17 (3)	13 (3)	30 (6)	8 (3)
Skin	45 (7)	46 (10)	10 (2)	13 (4)
Central Nervous System	11 (2)	12 (3)	16 (3)	5 (2)
Haematology	16 (3)	8 (2)	5 (1)	5 (2)
Endocrine	12 (2)	10 (2)	30 (6)	15 (5)
Locomotor	139 (22)	111 (25)	68 (14)	65 (22)
Ear/Nose/Throat	61 (10)	38 (8)	19 (4)	14 (5)
Opthalmic	39 (6)	30 (7)	12 (2)	13 (14)
Other	15 (2)	14 (3)	3 (1)	4 (1)
TOTAL NUMBER OF RECORDED ILLNESSES	616 (100)	449 (100)	496 (100)	297 (100)

Thus the benzodiazepine group had experienced significantly more episodes of major and minor systemic illness than the control group ($t = 5.14$, $df = 408$, $p < 0.001$; $t = 3.33$, $df = 408$, $p < 0.01$).

8.1.5.4 Consultation Rates.

For each of the last five years benzodiazepine patients consistently consulted their GP at a significantly higher rate than controls, as illustrated in Table 8.6.

8.1.5.5 Psychotropic Medication and Psychiatric Referral

Over the last ten years, benzodiazepine users had received a significantly greater variety of antidepressants ($t = 4.87$, $df = 408$, $p < 0.001$), major tranquillizers ($t = 2.50$, $df = 408$, $p < 0.05$), benzodiazepine anxiolytics ($t = 6.11$, $df = 408$, $p < 0.001$), benzodiazepine hypnotics ($t = 3.95$, $df = 408$, $p < 0.001$), and other psychotropics ($t = 3.77$, $df = 408$, $p < 0.001$), although the overall frequencies were relatively low. Over the same period the mean number of pharmacologically distinct non-psychotropics prescribed on at least one occasion for the benzodiazepine group was 11.41 (SD = 9.56), compared with 7.29 (SD = 6.00) for the control group, reflecting a significant difference between groups ($t = 4.73$, $df = 408$, $p < 0.001$).

Benzodiazepine patients were also currently receiving more antidepressants and non-psychotropic drugs ($t = 4.75$, $df = 408$, $p < 0.001$; $t = 8.01$, $df = 408$, $p < 0.001$), both of which had been prescribed for a significantly greater length of time in comparison

Table 8.6. Comparison of average number of GP consultations by year for BZ users and controls (df = 408)

Year	BZ Users Mean (SD)	Controls Mean (SD)	t	p<
1983	5.40 (6.06)	2.79 (3.99)	5.14	0.001
1984	6.45 (6.43)	3.24 (4.26)	5.96	0.001
1985	6.89 (6.18)	3.52 (4.43)	6.35	0.001
1986	6.60 (6.12)	4.05 (4.73)	4.71	0.001
1987	6.53 (5.83)	3.65 (4.38)	5.64	0.001
1983 - 1987	32.03 (25.76)	17.34 (16.87)	6.83	0.001

to controls ($t = 3.30$, $df = 408$, $p < 0.01$; $t = 4.52$, $df = 408$, $p < 0.001$).

Within the benzodiazepine group, 75 (36.5%) patients had previously received a psychiatric referral and 5 (2.4%) patients a psychological referral, in comparison with 13 (6.3%) patients and 1 (0.5%) patient respectively in the control group.

8.1.5.6 Sex Differences.

Within the benzodiazepine group the mean male age of 59 years (S.D. = 15 years, range = 29 - 90 years) was significantly lower than that of the mean female age of 65 years (S.D. = 13 years, range = 27 - 88 years) ($t = 2.83$, $df = 203$, $p < 0.01$). The only other differences between the sexes in benzodiazepine users were the greater overall number of previous major systemic illnesses ($t = 2.15$, $df = 203$, $p < 0.05$), minor respiratory illnesses ($t = 2.87$, $df = 203$, $p < 0.01$), and minor central nervous system illnesses ($t = 2.31$, $df = 203$, $p < 0.05$) in males, and the greater variety of previously prescribed anxiolytics for males ($t = 2.01$, $df = 203$, $p < 0.05$). Female benzodiazepine users suffered more previous episodes of minor genito-urinary illness ($t = 2.10$, $df = 203$, $p < 0.05$) than male counterparts.

Within the control group a similar age difference existed between the sexes given the matching of subjects. However, female controls had received, during the previous ten years, a significantly greater variety of antidepressants ($t = 2.43$, $df = 203$, $p < 0.016$), benzodiazepine anxiolytics ($t = 2.41$, $df = 203$,

$p < 0.017$) and non-psychotropics ($t = 2.04$, $df = 203$, $p < 0.043$) than the male counterparts. Females also suffered fewer episodes of major locomotor illness ($t = 2.51$, $df = 203$, $p < 0.013$).

8.1.5.7. Benzodiazepine Anxiolytics and Hypnotics

Table 8.7 illustrates the current distribution of benzodiazepine anxiolytic and hypnotic presciption. A total of 79 (38%) patients received 'anxiolytic' medication alone; 98 (48%) received 'hypnotic' medication alone, and 28 (14%) received 'anxiolytic plus hypnotic' medication. The total sample of 205 patients included two receiving repeat prescriptions concurrently for two different hypnotics, and three receiving two different anxiolytics.

One-way analysis of variance with post-hoc Scheffe comparisons was used to illustrate significant between group differences. Table 8.8 summarises the mean scores of variables that differed significantly between groups and presents the results of the statistical analysis.

Table 8.8 shows that patients currently receiving a benzodiazepine hypnotic alone were significantly older and had received their first benzodiazepine prescription at a later age than patients currently receiving a benzodiazepine anxiolytic alone, or a benzodiazepine anxiolytic plus hypnotic.

Table 8.7. Distribution of current repeat prescription benzodiazepines

Hypnotics		Anxiolytics	
Generic Name	No (%) of Patients	Generic Name	No (%) of Patients
Temazepam	59 (46)	Diazepam	56 (51)
Nitrazepam	57 (44)	Oxazepam	34 (31)
Triazolam	11 (9)	Lorazepam	13 (12)
Lormetazepam	1 (11)	Chlordiaze-poxide	7 (6)
TOTAL	128 (100)		110 (100)

Table 8.8. Means (SD) and summary of differences between benzodiazepine (BZ) hypnotic alone, anxiolytic alone, and anxiolytic + hypnotic groups (df = 2,202).

Variable	Group 1 Hypnotic (n = 98)	Group 2 Anxiolytic (n = 79)	Group 3 Anxiolytic + Hypnotic (n = 28)	F	P <	Scheffe
Patient age (yrs)	68.93 (12.27)	58.68 (13.16)	60.93 (12.90)	14.39	0.001	1-2,1-3
Age BZ first prescribed (yrs)	57.02 (13.05)	47.68 (14.07)	48.04 (12.16)	12.23	0.001	1-2,1-3
No. previous major + minor systemic illnesses	6.02 (4.02)	4.42 (3.12)	6.18 (4.30)	4.67	0.01	1-2
No. previous major systemic illnesses	2.79 (2.22)	1.86 (1.75)	2.68 (2.16)	4.84	0.01	1-2
No. previously prescribed non-psychotropic medications	12.70 (9.44)	9.05 (9.64)	13.57 (8.65)	4.14	0.01	1-2
No. previously prescribed hypnotics	0.52 (0.69)	0.38 (0.72)	0.86 (0.75)	4.65	0.01	2-3
No. currently prescribed medications	3.82 (2.35)	3.67 (2.12)	4.82 (2.14)	4.39	0.01	2-3

Key : Post-hoc Scheffe treatment group comparisons : 1 = Hypnotic; 2 = Anxiolytic; 3 = Anxiolytic + Hypnotic.
Note : Groups separated by a hyphen differ significantly from each other, $p<0.05$.

Furthermore, patients receiving a benzodiazepine hypnotic alone, when compared with the anxiolytic alone group had suffered a significantly greater number of major plus minor systemic illnesses, especially major, and had also received a significantly greater variety of non-psychotropic medications. The anxiolytic plus hypnotic group revealed similar scores to those of the hypnotic alone group on these three variables. The differences which emerged between the anxiolytic alone and the anxiolytic plus hypnotic groups were not significant, possibly due to the comparatively small size of the latter group.

Finally, the anxiolytic plus hypnotic group had previously received a greater variety of hypnotics and was currently receiving a greater overall number of medications than the anxiolytic alone group. This result can perhaps be explained by the dual nature of benzodiazepine prescription for the anxiolytic plus hypnotic group. However, no such differences emerged between the hypnotic alone and anxiolytic plus hypnotic groups.

8.1.6 Discussion.

The data for the present study were gathered from GP records and are therefore somewhat restricted in that information derived from personal interview and standardised assessment of patients is not reported. However an assessment of psychological ill-health, attitude towards benzodiazepine use, and willingness to stop or alter benzodiazepine medication was collected for a subsample of the benzodiazepine group and will be reported in Chapter 9.

Nevertheless the findings of the present study illustrate a number of important features of benzodiazepine users.

The data obtained from the three study practices confirm estimates of other researchers of extensive long-term use of benzodiazepines. The level of 26 long-term benzodiazepine users per 1000 patients, concentrated in the older age group, provides a substantial challenge to primary care.

The age and sex distribution of the benzodiazepine group is similar to that reported in previous studies (Salinsky and Dore 1987; Rodrigo et al 1988). However this is the first controlled study to report significantly greater specific systemic illness in what is the largest United Kingdom benzodiazepine group yet studied. Former studies have lacked controls or reported general levels of illness in single practices with sample sizes of about 70 subjects. The individual categories of disease that presented significantly more often in benzodiazepine users in the current study may repay more detailed investigation.

Benzodiazepine users exhibit higher rates of cardiovascular, respiratory, central nervous system, gastro-intestinal, genito-urinary, and to a lesser degree, ear, nose and throat illnesses than matched controls.

Explanations for such an excess could be the parallel treatment of discomfort or anxiety accompanying somatic pathology, or the presence of specific organic system vulnerability or weakness underlying the most commonly expressed symptoms of a given anxiety disorder as suggested by Malmo and Shagass (1949).

Another explanation may be that major systemic illness exacerbates the development of anxiety symptoms leading to a subsequent demand for benzodiazepine medication in patients with anxiety prone personalities. Alternatively doctors may experience difficulty helping patients to cope with a chronic physical complaint, and therefore prescribe benzodiazepines to try to alleviate the anxiety and/or despondency that the complaint engenders in the patient, and possibly in the doctors themselves. Further detailed interview and establishment of the precise sequence of physical illness, psychiatric sequelae, and subsequent prescription will be needed to clarify these alternatives.

The higher level of consultation in the benzodiazepine group may simply reflect attendance for repeat benzodiazepine prescription, although during the period studied repeat prescription could easily be obtained without GP consultation. Alternatively more frequent consultation could be related to the higher level of somatic morbidity rather than a lower tolerance of disease. However the benzodiazepine group also received a greater variety of psychotropic medication, which may reflect a higher incidence of psychiatric morbidity, or drug dependency, or poor alternative coping resources for both patients and doctors.

Male benzodiazepine users had suffered a greater overall number of previous major systemic illness than female benzodiazepine users. These sex differences were not present in the matched controls, so the sex difference in the benzodiazepine group cannot be wholly explained by the higher incidence of

systemic illnesses in males in general. However this conclusion should be treated with caution given the relatively small number of males in the present study.

A major finding of the present study is that significant differences exist between patients currently receiving a hypnotic alone, an anxiolytic alone, or an anxiolytic plus hypnotic.

The hypnotic alone users are the oldest group, and have suffered more previous systemic illnesses than those prescribed an anxiolytic alone. These results suggest that benzodiazepine hypnotics may be prescribed if patients' sleep is disrupted by serious illness, the process of ageing, or both.

The characteristics of long-term benzodiazepine users, in the present study, reflect a picture of ill-health in a predominantly aged population. It is interesting to note that the mean age of patients receiving their first benzodiazepine prescription was 47 years, which is arguably older than the suggested age of onset for the anxiety disorders, which are predominantly regarded as occurring in early adulthood.

It is currently accepted that long-term benzodiazepine use is not recommended for the treatment of anxiety states or insomnia (Committee on the Review of Medicines 1980), and there is growing pressure for patients to be withdrawn from long-term use. However issues affecting first-time prescription must be distinguished from the approach to current long-term users. The present study highlights the confounding influence of major somatic morbidity in a population of long-term users. The need for further

investigation of the interrelationship between benzodiazepine prescribing and physical illness is required and may need to be addressed separately from the issues surrounding long-term use in anxiety states. Furthermore the implementation of graded-withdrawal programmes for long-term benzodiazepine users must attempt to address such issues, as different management strategies may be necessary for those long-term benzodiazepine users characterised by chronic physical illness, as opposed to those who are in relatively good health. The balance of benefit and risks between steady-state moderate long-term use of hypnotics in physically ill older patients also needs to be addressed separately from that of users who are young and free from such somatic problems.

The challenge which long-term use of benzodiazepines presents to the medical professions and patients is large and real. However, the response should be a careful and measured one. Patients should not be stressed by ill-prepared abrupt withdrawal, carried out as a response to media and legal pressure, in the absence of adequate support strategies . Further research into the use of alternative graded-withdrawal programmes in primary care settings will be required before clear guidelines can be formulated on the best form of management of these patients.

Whilst GP records have provided clear evidence with regard to physical morbidity there is a lack of clarity relating to psychological ill-health and willingness to reduce or alter

benzodiazepine intake. An attempt to gather such information is presented in the following chapter.

CHAPTER 9 : TERTIARY STUDY

9.1.1 Psychological ill-health and attitude to benzodiazepine use and withdrawal among long-term benzodiazepine users.

Rodrigo et al (1988) stated that their one general practice, sixty-four patient sample, was the first study of "long-term benzodiazepine users in which a standard assessment of psychiatric morbidity has been carried out." They used the Clinical Interview Schedule (CIS) (Goldberg et al 1970), the Kellner and Sheffield (1973) Symptom Rating Test (SRT), asked patients questions about their past and present use of medicines, and extracted information on physical ill-health from GP records. Although this study has methodological limitations, it is to be commended in attempting to interview long-term benzodiazepine users to assess formal psychiatric diagnosis according to ICD criteria using the CIS. However only 2 of 16 male subjects and 20 of 48 female subjects were able to be classified as CIS cases, the most common diagnosis being 'neurotic depression', accounting for 1 male and 16 female subjects. While this study reported SRT scores no other anxiety or depression measure of psychological ill-health was reported.

Although the prescribing of benzodiazepines has been reportedly associated with social problems (Kedward 1969; Cooper 1972; Cooper and Sylph 1973; Cooperstock and Lennard 1979) systematic research has failed to evaluate the specific social difficulties that characterise such patients. Furthermore the

level of social problems experienced by benzodiazepine users in comparison to other relevant groups has not been assessed.

Current high level media coverage has presented a negative view of benzodiazepines by highlighting dependence and recommending withdrawal. While some groups of benzodiazepine patients are presently taking legal action against the prescribers and manufacturers of such drugs, there has been little systematic research on the attitudes of patients who are currently on long-term medication. In an attempt to clarify some of these issues the psychological ill-health and attitude to benzodiazepine use and withdrawal among long-term benzodiazepine users was investigated in more detail.

9.1.2 Subjects

From the sample of 445 benzodiazepine anxiolytic and/or hypnotic users described in section 8.1.2, a random sample of 145 patients was contacted. They were sent a letter on practice notepaper, signed by a research administrator (VS) on behalf of their GP, inviting them to attend their own health centre to discuss their treatment on benzodiazepines. The invitation in no way suggested that attendance would result in their being withdrawn from benzodiazepine medication (Appendix 9).

9.1.3 Procedure

Two research assistants (ECS and DS) were trained by the current author to conduct a semi-structured interview and to administer a number of standard assessment measures to each patient

who attended for a forty-five minute assessment session.

9.1.4 Measures

Three primary self-report questionnaires of psychological ill-health were used:

a) The Kellner and Sheffield (1973) Symptom Rating Test (SRT) as used in sections 6.1.4, 6.2.4, and 7.1.4..

b) The General Health Questionnaire (60-item) (GHQ) (Goldberg 1972) as used in section 7.1.4..

c) The Beck Depression Inventory (BDI) (Beck et al 1961) was used to assess behavioural manifestations of depression. The BDI consists of 21 categories of symptoms and attitudes. Each category describes a specific behavioural manifestation of depression and consists of a graded series of self-evaluative statements (Appendix 10). Beck et al (1961) reported a split-half reliability of +0.86 for the inventory, and high degrees of validity when compared with diagnostic judgements of clinicians.

In addition one interviewer/assessor questionnaire of psychological ill-health was used:

d) The Hamilton Anxiety Scale (HAM-A) (Hamilton 1959) as used sections 6.1.4, 6.2.4,and 7.2.4..

In addition patients completed three other questionnaires:

e) The Social Problems Questionnaire (SPQ) (Corney and Clare 1985). Designed to measure the presence/absence of social problems, the questionnaire covers housing, occupation, finance, social and leisure activities, child/parent and marital

relationships, relationships with relatives, friends, neighbours and workmates, and legal problems (Appendix 11).

f) A 'Benzodiazepine Dependency Questionnaire' (BZDQ) constructed by the present author to assess patients' attitudes to their current benzodiazepine medication, for example, willingness to stop or change medication, concern at being on medication, appropriateness of current dosage etc. (see Appendix 12).

9.1.5 Results

From a total of 48 patients who attended for interview, 44 (31 female, 13 male) completed all the assessment measures. Of this sample, 10 were receiving 'anxiolytic + hypnotic' medication; 16 were receiving an 'anxiolytic alone', and 18 were receiving a 'hypnotic alone'. A significant between-group difference existed for age ($F(2,43) = 3.56$, $p < 0.05$), as illustrated in Table 9.1., although no two groups differed significantly at the 0.05 post-hoc Scheffe level. Length of time on repeat prescription benzodiazepines did not differ between benzodiazepine subgroups ($F(2,43) = 1.31$, $p = 0.278$). Males and females did not differ with respect to age ($t = 0.55$, $df = 42$, $p = 0.588$) or length of time on repeat prescription benzodiazepines ($t = 0.70$, $df = 42$, $p = 0.491$).

Table 9.1 Means, standard deviations, (SD) and one-way analysis of variance between hypnotic alone, anxiolytic alone, and anxiolytic + hypnotic groups (df = 2,41).

Variable	Hypnotic (N = 18)	Anxiolytic (N = 16)	Anxiolytic + Hypnotic (N = 10)	F	P
Age	60.61 (12.98)	52.50 (8.83)	62.30 (7.60)	3.56	0.037*
Length of time on benzodiazepines (mths)	138.22 (119.41)	83.87 (85.73)	107.20 (66.36)	1.31	0.278
HAM-A	9.77 (6.76)	9.25 (6.32)	8.20 (6.52)	0.18	0.830
SRT	15.55 (13.72)	14.81 (13.54)	13.20 (13.99)	0.10	0.903
GHQ	8.05 (14.92)	6.00 (8.73)	8.40 (13.25)	0.15	0.857
BDI	7.61 (7.38)	4.87 (5.35)	5.60 (5.92)	0.82	0.444

* $p < 0.05$

Key : Post-hoc Scheffe treatment group comparisons : 1 = Hypnotic; 2 = Anxiolytic; 3 = Anxiolytic + Hypnotic.

Note : Groups separated by a hyphen differ significantly from each other.

a) Psychological Ill-Health: Table 9.1 also presents the HAM-A, GHQ, and BDI scores for the 'anxiolytic + hypnotic', 'anxiolytic alone' and 'hypnotic alone' groups. No significant between-group differences on these variables were found by one-way analysis of variance.

Given that the benzodiazepine treatment subgroups failed to differ on the measures of psychological ill-health (Table 9.1), and that no significant sex differences existed (see Table 9.2), the remainder of the results section will present data for the benzodiazepine group as a whole. Table 9.3 presents the overall group means and standard deviations on the HAM-A, SRT, GHQ, and BDI.

From the total sample of 44 patients interviewed, only 11 (25%) scored $\geq$ 15 on the HAM-A and were therefore within the range required to satisfy the HAM-A entry criterion which operated in the main study (Chapter 7). The proportion of patients who scored > 12 on the SRT was 43%. This is similar to Rodrigo et al's (1988) figure of 50% for their sample of 64 long-term benzodiazepine users. In the present study only 5 patients (11%) achieved a score of > 19 on the GHQ, a level at which it is suggested that patients will only improve if offered treatment (Johnstone and Goldberg 1976).

All measures of psychological ill-health showed significant positive correlations with one another as shown in Table 9.4.

b) Social Problems: Table 9.5 gives the results of the present study and other relevant work (Corney and Clare 1985) for

Table 9.2 t-tests between male and female benzodiazepine patients on HAM-A, SRT, GHQ and BDI (df = 42)

	Male	Female		
	(N = 13)	(N = 31)		
Variable	Mean (SD)	Mean (SD)	t	p
HAM-A	9.15 (6.74)	9.25 (6.40)	0.05	0.962
SRT	6.38(13.26)	7.80(12.15)	0.34	0.732
GHQ	13.23(15.01)	15.06(12.93)	0.41	0.684
BDI	5.30 (7.30)	6.51 (6.01)	0.57	0.571

Table 9.3 Means and standard deviations (SD) on HAM-A, SRT, GHQ, and BDI for all repeat prescription benzodiazepine interviewees (n = 44).

Variable	Mean	SD
HAM-A	9.22	6.43
SRT	14.52	13.43
GHQ	7.38	12.35
BDI	6.15	6.36

Table 9.4. Pearson Correlation Coefficients for all repeat prescription benzodiazepine interviewees on HAM-A, SRT, GHQ, and BDI (df = 44).

	HAM-A	SRT	GHQ	BDI
HAM-A		0.873*	0.593*	0.711*
SRT			0.669*	0.807*
GHQ				0.804*
BDI				

(* p <0.001)

Table 9.5. Numbers of different types of SPQ problems per person by sample.

Number of different types of major problems per person	*Sample from GP List Male (%) (n=68)	Female (%) (n=90)	*GP Attenders Outer London (%) (n=81)	Inner London (%) (n=94)
None	70.6	63.3	53.1	41.5
One	14.7	18.9	21.0	23.4
Two	10.3	10.0	17.3	13.8
Three	1.5	4.4	4.9	10.6
Four+	2.9	3.3	3.6	9.5

Number of different types of major problems per person	*Psychiatric out-patients (%) (n=27)	*Social Worker referrals (%) (n=65)	Present Study (%) (n=44)
None	40.7	3.1	79.5
One	14.8	24.6	11.4
Two	14.8	27.7	2.3
Three	18.5	20.0	4.5
Four+	11.1	24.6	2.3

*(Corney and Clare 1985)

comparison. The repeat prescription benzodiazepine patients showed a similar SPQ profile to that exhibited by Corney and Clare's (1985) random sample from a GP list. Social work referrals, psychiatric out-patients, and GP attenders all showed higher levels of major social problems than repeat prescription benzodiazepine users. The most common problem identified by the benzodiazepine users was interpersonal relationship problems (9.0%), followed by work (7.0%),and marital (7.0%) difficulties. However in general the SPQ data did not support the notion that those repeat prescription benzodiazepine users who attended for assessment interview suffered from unusually high levels of social problems.

c) Attitude to Benzodiazepine Use: Table 9.6 shows the replies of patients to the BZDQ. Over 80% of patients regarded their medication as being vital/essential or very important in helping them cope. Only a minority of patients (11% approx.) were definitely, or very much concerned about being on benzodiazepines, and over 70% thought that it would be fairly, or very difficult to stop medication. Over 80% thought that their current benzodiazepine dosage was just about right. Given the above picture it may seem surprising that approximately 40% of patients stated that they were fairly or very willing to stop their medication. However it must be remembered that the remaining 60% were fairly or very unwilling to cease benzodiazepine medication. Similarly, approximately 68% expressed some degree of concern if their medication were to be changed. It therefore

Table 9.6. Responses to 'Benzodiazepine Dependency Questionnaire' (n = 44)

Question 1 :
How important is your medication in helping you cope ?

Response	%
Vital/essential	34.1
Very important	47.7
A little important	13.7
Not important	4.5

Question 2 :
Does being on your medication concern you at all ?

Response	%
Not concerned at all	54.5
A little concerned	34.1
Definitely concerned	9.1
Very much concerned / worried	2.3

Question 3 :
How easy do you think it would be to stop your medication ?

Response	%
Very easy	4.5
Fairly easy	22.7
Fairly difficult	29.5
Very difficult	40.9
(Don't know	2.3)

Question 4 :
What do you think about your current medication dosage ?

Response	%
Extremely high	0
A little high	9.1
Just about right	81.8
Extremely low	9.1

Table 9.6 Responses to 'Benzodiazepine Dependency Questionnaire' (contd)

Question 5 :
How willing would you be to stop your medication ?

Response	%
Very willing	13.6
Fairly willing	27.3
Fairly unwilling	40.9
Very unwilling	18.2

Question 6 :
How do you think you would feel if your medication was changed ?

Response	%
Not concerned at all	31.8
A little concerned	36.4
Definitely concerned	25.0
Very much concerned/ worried	6.8

Question 7 :
How do you think you would feel if your medication was stopped ?

Response	%
Not concerned at all	6.8
A little concerned	13.6
Definitely concerned	36.4
Very much concerned / worried	40.9
(Dont know	2.3)

seems consistent that about 81% reported some degree of concern if their medication were to be stopped.

9.1.6 Discussion

Unfortunately only 44 patients, representing 30.3% of the original 145 invited patients, attended for interview; so any generalisations from the present study should be treated with caution. A number of factors may have contributed to the poor response rate in this study. Although the invitation letter (Appendix 9) deliberately did not suggest that attendance would result in patients being withdrawn from medication, patients may have feared that attendance would result in benzodiazepine withdrawal, and therefore have decided not to attend. If this is so then the figures on benzodiazepine dependency, willingness to modify or stop medication, etc. may present an over-optimistic picture as those who failed to attend may be more heavily benzodiazepine dependent.

Mellinger et al (1984) suggested that long-term, predominantly benzodiazepine anxiolytic users exhibit high levels of psychic distress, in particular anxiety and depression. Murray (1981) from her'Woman's Own' postal survey reported that 83 % of self-selected psychotropic drug users scored > 12 on the SRT. Similarly, Williams et al (1982) reported that 84 % of male and 91 % of female, newly prescribed psychotropic drug users scored > 12 on the SRT and were therefore classified as "probable psychiatric cases". The number of patients achieving this

cut-off on the SRT in the present study was substantially lower than the figures cited by Murray (1981) and Williams et al (1982). The trend towards a low percentage of psychiatric or psychological 'caseness' in the present study was further strengthened by the relatively low HAM-A and GHQ scores. The low number of patients achieving 'caseness' scores on the various assessment measures may suggest that long-term benzodiazepine use is functional in reducing anxiety-related symptoms. Alternatively, if (as suggested in Chapter 8) long-term benzodiazepine use is associated primarily with a history of major systemic illness, it may be that the group of long-term users in this study has never shown exceptionally high levels of psychiatric and psychological morbidity. Further work is needed to clarify whether, in this long-term benzodiazepine group, the original benzodiazepine prescription was aimed at purely psychological, physiological, or a combination of presenting symptoms.

Approximately 80% of the present study population reported no major social problems. This finding is at odds with the popular stereotype of the long-term benzodiazepine user, but probably concurs with the data presented in Chapter 8, which show benzodiazepine users characterised as a predominantly elderly population with a history of major systemic illness. However the high percentage of patients who failed to attend for interview may be even more heavily benzodiazepine dependent than the study sample. Similarly, non-attendance may have been higher in patients with greater psychiatric morbidity and major social

problems. Indeed these characteristics may predispose towards non-attendance in such studies.

The picture presented by patients' replies to the BZDQ suggests a dependence on and concern about alteration or cessation of a level of benzodiazepine usage that is regarded as 'just about right'. Forty per cent of the sample were fairly or very willing to stop benzodiazepine medication, but ironically 77% expressed concern if their medication were to be stopped. This may suggest that a substantial number of benzodiazepine users, while regarding themselves as dependent on their medication, and worried about how they would cope without such medication, would still consider some form of graded, structured, and medically supervised withdrawal package. Although not presented, the patient group exhibited a level of benzodiazepine intake that was usually below the originally prescribed dosage. As such they did not appear as a long-term, high-dosage, benzodiazepine abusing group. Rather they appeared to have altered their dosage to the lowest, most appropriate, level. The results of this study, and the data presented in Chapter 8, may have implications for the implementation of withdrawal programmes that are currently receiving support and attention. This will be discussed in more detail in the following final chapter.

CHAPTER 10 : DISCUSSION

A thorough review of the literature highlighted specific gaps in our knowledge of pharmacological and psychological aspects of anxiety management. The work undertaken for this thesis was designed to redress the situation with a series of studies aimed at answering specific questions in the hope that the answers would have clinical relevance to anxiety management.

The results of the Pilot Study 1a suggested that anxiety recurrence and withdrawal symptoms occur in a significant proportion of patients after a relatively short period of benzodiazepine treatment. The potential for dependence on benzodiazepines may be explained by these phenomena. However it is not just the occurrence of withdrawal symptoms and the recurrence of anxiety that may lead to pharmacological dependence. It has been suggested that the best predictor of susceptibility to drug dependence and subsequent withdrawal symptoms is a passive and dependent personality (Tyrer et al 1983). Such traits are likely to be prevalent in anxiety patients thereby increasing their propensity to drug dependency. Furthermore patients' interpretation of the significance of somatic changes during, or following, benzodiazepine withdrawal is also an important factor influencing drug dependence. Following the reduction or cessation of a successful anxiolytic compound some patients may interpret any minor withdrawal symptoms and/or slight increases in anxiety as

evidence of an exacerbation of their original anxiety state. They may then revert to pharmacological treatment by requesting renewed prescription, as their only method of alleviating anxiety symptoms. This is likely to lead to feelings of inability to cope without medication and may further exaggerate any feelings of helplessness and dependency. If however withdrawal symptoms are regarded as temporary, independent of anxiety state, and part of the process of the body readjusting to functioning without an active anxiolytic, then this is less likely to foster dependency. However following a limited treatment period with diazepam, withdrawal symptoms and anxiety recurrence can be minimized by withdrawing the drug in a gradual manner as was shown in the Main Study. Since it is not easy to identify which patients are at risk of suffering withdrawal symptoms and possible dependency problems, graded-withdrawal should be a standard procedure for all patients. Using graded-withdrawal enhances the effectiveness of benzodiazepine treatment and diminishes the risk of dependency.

There has been an increasing preference for using short half-life benzodiazepines. This decision may be premature and unwarranted if ongoing research substantiates the viewpoint that benzodiazepines with shorter half-lifes are associated with greater dependency - their withdrawal symptoms occur earlier, and are often more severe - than longer-acting alternatives (Tyrer and Murphy 1987). Consequently it may be judicious, in some cases, for patients to be changed from short- to long-acting benzodiazepines prior to graded-withdrawal. Nevertheless there will be a

substantial number of patients for whom withdrawal effects and/or psychological dependence are either very severe or have such an intense personal impact that it would be unethical to pressurise them into stopping medication. The results of such action may be worse than the original condition. Jenner (1985) stated that "we should not fight too hard to stop patients taking the tablets they believe in". Another option should be available for those patients who are able to stop regular consumption but find it difficult to cope without the occasional tablet, - that of maintenance on flexible, intermittent low dosage. This option may be particularly applicable to the long-term benzodiazepine users (especially of hypnotics) in the older age group and characterised by a high incidence of previous major systemic illness, who comprised a large proportion of the study group reported in Chapter 8. To impose a blanket withdrawal programme for all such patients may be impractical and unethical. As an alternative, long-term benzodiazepine patients should be screened in order to assess self-motivation and suitability for graded-withdrawal. In Chapter 9 it was suggested that although patients are concerned about their benzodiazepine medication being stopped a significant minority would nonetheless be willing to consider ceasing medication, presuming some form of structured graded-withdrawal programme were operative.

The development of alternative coping strategies and anxiety management techniques may prove useful prior to and during withdrawal programmes. For example, individual patients may

benefit from relaxtion training prior to withdrawal. However Cormack and Sinnott (1983) suggest that these techniques are not helpful as methods of reducing dependency when used in group settings. In addition relaxation training alone is unlikely to suffice as an adequate coping strategy. Cognitive strategies - teaching the patient to reappraise and alter their perception of the significance of withdrawal symptoms - should be incorporated as a major treatment component of any withdrawal package. Patients should be prevented from spectating on themselves for withdrawal symptoms and should refrain from exaggerating or catastrophising the significance of any minor somatic change. In patients with specific anxiety problems, as well as withdrawal difficulties, formal psychological treatment may be necessary. However the effectiveness of psychological interventions during withdrawal have yet to be fully evaluated.

An increasing number of reports point to the efficacy of anti-depressants for the treatment of anxiety states (Klein et al 1983; Telch et al 1985; Michelson and Mavissakalion 1985). However the efficacy of anti-depressants during withdrawal from long-term benzodiazepines has not been published. Recent evidence (reported by K. Rickels at the British Association of Psychopharmacology in December 1987) suggests that long-term benzodiazepine users whose withdrawal is covered by parallel anti-depressant therapy are more likely to remain benzodiazepine abstinant at 6 to 12 months follow-up. Tyrer (1985) has also suggested that anti-depressants may be useful during benzodiazepine withdrawal. Controlled

investigations of the efficacy of different types of psychological support, and anti-depressant and placebo covered withdrawal, during graded-withdrawal from long-term benzodiazepine use, are in the process of being implemented by the current author and his colleagues.

This series of studies was commenced prior to publication of DSM III-R, and hence the DSM-III definition of GAD was used throughout. However patients included in the present studies would in fact have met all but one of DSM III-R GAD criteria. DSM III-R GAD diagnosis states that "unrealistic or excessive anxiety and worry" be present for at least a 6-month period. This contrasts with the minimum one month recommendation for DSM-III GAD symptoms. In all treatment groups in the present studies the average minimum duration of symptoms was > 3 months. So the GAD patients studied were not experiencing transitory, episodic symptoms of anxiety, but were a group of patients with a chronicity of symptoms greater than that necessary to meet DSM-III criteria. This study suggests that on average GAD patients attempt to cope with their anxiety symptoms for approximately 3 months before seeking medical assistance. To expect GAD patients to suffer these symptoms for up to 6 months, without some form of pharmacological or psychological treatment, in order to meet DSM III-R GAD criteria, seems unethical. If DSM III-R criteria had been implemented it would have been difficult to recruit the number of patients, drug-free at study inclusion and who had not been using benzodiazepines for protracted periods prior to referral,

necessary for the present studies. It therefore seems that the DSM III-R GAD definition imposes an excessively long time criterion for a disorder that is both prevalent and disabling in the short- and long-term.

The present series of studies has also shown that a prescription for benzodiazepines is not the only form of management for GAD patients. The 'Cognitive-Behaviour Therapy' (CBT) used in the present series of studies was similar to Butler et al's (1987a) 'Anxiety Management' (AM) treatment. Butler et al (1987a) stated that this form of treatment is "brief and simple" and is "clearly suitable for patients with persistent GAD, who are commonly seen in general practice for whom prolonged drug treatment is unsatisfactory". These authors also regard this treatment approach as easy to teach to therapists and readily understood by patients. They note that it has a sound rationale "because, as well as including procedures for controlling symptoms, it deals with anxious cognitions and avoidance behaviour, both of which contribute to the maintenance of anxiety disorders". It seems reasonable to expect that a treatment approach that addresses the three main components of anxiety (Lang 1971) would produce greater and more stable degrees of clinical improvement than techniques that are aimed at purely cognitive (Beck and Emery 1979), primarily somatic (Lehrer 1978), or mainly behavioural (Durham and Turvey 1987) aspects of GAD management. Whether or not the most appropriate term for this eclectic and pragmatic psychological treatment approach for GAD is 'Anxiety Management' or 'Cognitive-

Behaviour Therapy' is debatable. The most important factor is that this treatment approach is effective.

The CBT approaches used in the present series of studies were more effective than the pharmacological alternatives at the end of the study period and at follow-up. However the superiority of CBT techniques did not become evident until approximately 28 days after the initiation of treatment. It therefore appears that GAD patients initially will do equally well whether inert or active pharmacological treatment, or psychological treatment is offered. If CBT techniques involve patients actively learning to control their anxiety symptoms and to develop new adaptive coping strategies, then it is hardly surprising that this is not achieved overnight. Although the benefits of CBT require time to become manifest they are well maintained at follow-up. It is planned that the 101 patients included in Chapter 7 will be followed-up for longer than the 6-month period already reported.

The current series of studies did not investigate prognostic indicators of treatment outcome. Butler and Anastasiades (1988) have very recently suggested that the response of GAD patients to 'Anxiety Management' was better if patients were less anxious and relatively less demoralised prior to treatment. They regarded 'demoralisation' as low self-esteem and failure to cope with symptoms. They also noted that demoralisation may impair treatment progress more than mild depression, especially if a patient's resources for coping are limited or under-used. The

CBT administered in the present series of studies may be effective not only because it alleviates the immediate somatic, cognitive, and behavioural symptoms of GAD, but also because it enhances patients' feelings that they can cope, and thereby improves their self-esteem.

The present studies have assessed in detail the relative effectiveness of different treatment approaches in the management of GAD. Further research should concentrate on the identification of clusters of symptoms, or patient characteristics, which preferentially predispose to positive treatment outcome with differing pharmacological and psychological treatment approaches. This would allow identification of the significant minority of patients who respond positively to benzodiazepine medication. As psychological treatment in the form of CBT is not always available nor always necessary, differential treatment based on reliable prognostic assessment would allow better use of G.P. and psychologist time and National Health Service resources.

Previous studies have attempted to determine the relative efficacy of cognitive and behavioural approaches in the management of GAD (Durham and Turvey 1987). The present research has deliberately avoided such comparisons, and instead addressed the basic question of how pharmacological and psychological treatments compare. It is hoped that this study has made some contribution to our understanding of the psychological and pharmacological

treatment options for the management of GAD, and that the information derived from this research will lead to more effective management of anxiety disorders in primary care.

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APPENDIX 1

HAMILTON RATING SCALE FOR ANXIETY

Hamilton Rating Scale for Anxiety

DATE OF EVALUATION	PT.NO. _____
_____	INITIALS _____

For each item check the one response which best characterizes the patient now.

	0 Not present	1 Mild	2 Moderate	3 Severe	4 Very severe
ANXIOUS MOOD Worries, anticipation of the worst, fearful anticipation, irritability					
TENSION Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax					
FEARS Of dark, of strangers, of being left alone, of animals, of traffic, of crowds					
INSOMNIA Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors					
INTELLECTUAL Difficulty in concentration poor memory					
DEPRESSED MOOD Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing					
SOMATIC (Muscular) Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone					
SOMATIC (Sensory) Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation					

DATE OF EVALUATION	PT. NO. -------
----------	INITIALS -------

HAM-A

	0 Not present	1 Mild	2 Moderate	3 Severe	4 Very severe
CARDIOVASCULAR SYMPTOMS Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, sighing, dyspnoea					
RESPIRATORY SYMPTOMS Pressure or constriction in chest, choking feelings, sighing, dyspnea					
GASTROINTESTINAL SYMPTOMS Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation					
GENITOURINARY SYMPTOMS Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence					
AUTONOMIC SYMPTOMS Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair					
BEHAVIOUR AT INTERVIEW Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.					

APPENDIX 2

HAMILTON ANXIETY GLOSSARY

ASSESSMENT OF ANXIETY STATES

GLOSSARY FOR USE WITH THE HAMILTON ANXIETY SCALE

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INTRODUCTION

The Hamilton Anxiety Scale and Glossary are intended for use with patients already diagnosed as suffering from neurotic anxiety states, and not for assessing anxiety in patients suffering from other disorders.

A series of symptoms is assembled to form the fourteen items of the scale, each of the items being defined in a series of brief statements and headed by the name of the item.

Examples of questions to elicit the severity of symptoms are written into the glossary. In addition the examiner will usually wish to ask other questions which are not written into the glossary, either general probes or more specific questions, depending on the nature of the patient's replies.

Assessments are made on a five point scale, examples of scoring criteria for each grade being included. In practice, the last grade is rarely used for out-patients, and serves more as a marker, a method of delimiting the range, rather than as a grade of frequent practical use.

The interviewer should introduce himself briefly, describe the purpose of the interview and explain any recording equipment.

(1) Anxious Mood (0-4)

Anxious mood may be regerded as a continuous state of apprehension pervading all situations. Milder anxious mood is relieved, at least in part, by certain aspects of the environment such as familiarity or company. It is important to remember that patients interpret the word "anxious" in all sorts of ways. Useful common terms are "nerves", "jittery", "on edge" "tense", or "up-tight".

" NOW, I WOULD LIKE TO ASK YOU ABOUT THE WAY YOU HAVE BEEN FEELING DURING THE LAST WEEK. HAVE YOU BEEN ON EDGE, OR HAD TROUBLE WITH YOUR NERVES? HAVE YOU BEEN FEELING ANXIOUS OR FRIGHTENED, AS THOUGH SOMETHING TERRIBLE WERE ABOUT TO HAPPEN TO YOU? HOW OFTEN? DOES IT COME AND GO? HOW LONG DOES IT LAST? HOW BAD IS IT? HOW MUCH DOES IT TROUBLE YOU? HAVE YOU BEEN IRRITABLE? HOW DO YOU SHOW IT?""

0 = Absent

1 = Mild. Inappropriate apprehensions or worries which are mild and present some of the time. a minor increase in irritability which occurs occasionally.

2 = Moderate. Moderately severe symptoms, present much of the time which are of concern to the patient and result in minimal impairment to social functioning or work performance. Patient irritable much of the time.

3 = Severe. Severe symptoms which are present most of the time or intermittent panic attacks impairing social functioning or work performance. Irritable most of the time and shows anger by shouting or quarelling.

4 = Very Severe. Persistent state of intense anxiety or intermittent severe panic attacks causing marked limitation of the patient's activities. Constantly irritable with violent outbursts of temper, possibly involving breaking objects or physical violence.

(2) Tension (0-4)

Patients may complain of tension in a variety of ways. They may complain of feelings of tension, inability to relax, being startled easily, weeping easily, trembling and shaking, and feeling restless.

" HAVE YOU FELT TENSE OR FOUND IT DIFFICULT TO RELAX DURING THE PAST WEEK? HAVE YOU BEEN "JUMPY" OR "SHAKY" OR "FIDGETY" AND "RESTLESS" DURING THE PAST WEEK? HAVE YOU BEEN MOVED TO TEARS DURING THE PAST WEEK? HOW MUCH AND HOW OFTEN HAVE THESE SORTS OF THINGS BOTHERED YOU? "

0 = Absent.

1 = Mild. Reporting a mild inability to relax on occasion. However a change in environment or company tends to relieve such tension.

2 = Moderate. Reporting a moderate inability to relax and feelings of restlessness occurring much of the time. Not alleviated by a change of environment or company.

3 = Severe. Reporting a marked inability to relax and feelings of restlessness present most of the time.

4 = Very severe. A constant feeling of needing to be on the move. A total inability to relax. Patient rarely stays seated for more than a short period of time.

(3) Fears (0-4)

Rate any specific fear that the patient reports e.g. fears of dark, strangers, being left alone, large animals, traffic, crowds, etc. Assess what restrictions the "fear" imposes on the patient.

" IS THERE ANY PLACE, SITUATION OR THING THAT YOU ARE AFRAID OF, THAT YOU TEND TO AVOID IF POSSIBLE, OR THAT MAKES YOU FEEL ILL AT EASE. "

0 = Absent.

1 = Mild. An irrational fear or foreboding of situations which are not avoided and can be approached with apprehension.

2 = Moderate. A moderate fear of situations, sometimes provoking panic. The patient prefers to avoid these situations but can approach if accompanied or if the situation demands.

3 = Severe. A severe fear of situations provoking panic and is almost always avoided, unless accompanied or unless sheer necessity requires that the situation be approached.

4 = Very severe. A very severe fear of situations which would produce total avoidance and which would produce a severe panic reaction if it were encountered.

(4) Insomnia (0-4)

Sleep disturbance may manifest itself in differing forms. Insomnia may present as:

difficulty falling asleep
broken or disturbed sleep (which is often difficult to assess)
early wakening

Patients may also complain of unsatisfactory sleep and fatigue on wakening, nightmares, dreams, and restlessness. When insomnia is severe it generally affects all phases of sleep and tends not to be relieved by hypnotics. Insomnia should be assessed on the degree to which sleep is lost over the course of the whole night compared with what may be normal for the population and the age-group.

" WHAT HAS YOUR SLEEP BEEN LIKE OVER THE LAST WEEK? HAVE YOU BEEN TAKING SLEEPING PILLS? WHAT TIME DO YOU GO TO BED? WHAT TIME DO YOU GO TO SLEEP? WHEN YOU DO GET TO SLEEP DO YOU SLEEP WELL? WHAT TIME DO YOU WAKEN IN THE MORNING? WHAT TIME DO YOU NEED TO GET UP? "

0 = Absent.

1 = Mild. Sleep loss of one hour or less, causing only minor concern to the patient.

2 = Moderate. Sleep loss of one to two hours, resulting in a degree of impaired social functioning or work performance that is of concern to the patient.

3 = Severe. Sleep loss of two to four hours, of much concern to the patient, and significantly impairing daily routine.

4 = Very severe. Sleep loss of greater than four hours and sleep only occurring in brief exhausted snatches. Severe functional impairment of daily routine tasks.

(5) Intellectual (cognitive) (0-4)

Intellectual and cognitive changes may manifest themselves as periods of forgetfulness, or complaints of inability to concentrate adequately.

" HAVE YOU HAD ANY DIFFICULTY CONCENTRATING AT WORK, OR ON OTHER THINGS YOU DO, E.G. HOBBIES, READING, WATCHING T.V., HOUSEWORK, DAILY CHORES. HOW OFTEN? HOW BAD IS IT? WHAT IS YOUR MEMORY LIKE? HAVE YOU NOTICED A CHANGE IN YOUR ABILITY TO REMEMBER THINGS?

0 = Absent.

1 = Mild. A minor increase in forgetfulness or concentration but not persistent and performance can be improved with added effort. No significant impairment in performance.

2 = Moderate. An increase in forgetfulness or concentration thereby impairing routine performance e.g. forgetting telephone numbers, inability to concentrate fully on T.V., reading or work. Results in a minor degree of impairment.

3 = Severe. A marked reduction in the ability to concentrate or remember, restricting the patient's daily performance. Routine tasks may be lengthened or not completed. The impairment is noticeable to others and unable to be overcome by the patient.

4 = Very severe. Unable to perform any series of routine tasks, or learn new information, due to a severe inability to concentrate or remember new information. Severely impaired.

(6) Depressed Mood (0-4)

Depressed mood may be characterized by a gloomy attitude, pessimism about the future.and feelings of hopelessness. Milder depressive mood may be relieved, at least in part, by environmental change, such as company or other forms of external stimulation. Patients may interpret"depressed mood" in different ways. Useful common phrases are"feeling down"or"feeling low".

" HAVE YOU BEEN FEELING REASONABLY CHEERFUL DURING THE PAST WEEK OR HAVE YOU FELT DEPRESSED OR LOW SPIRITED? HOW WOULD YOU DESCRIBE IT? DOES IT COME AND GO? HAVE YOU LOST INTEREST IN THINGS? DO ANY ACTIVITIES GIVE YOU PLEASURE? DO YOU FEEL BETTER OR WORSE AT ANY TIMES OF THE DAY?

0 = Absent. Very mild or occasional feelings no worse than the patient's normal experience when well.

1 = Mild. Persistent feelings described as moody, downhearted or dejected. More intense occasional feelings may be relieved by company,or a change in environment, or in a change in activity.

2 = Moderate. Persisting or frequent feelings of depression, blueness, etc.; often feels like crying, may cry occasionally, not easily relieved by company or environmental change.

3 = Severe. More intense feelings; frequent bouts of crying and feelings of despondency and helplessness throughout the working day.

4 = Very severe. Persistent severe feelings, may be described as beyond tears, painful, no relief, excruciating, agonising, persistent, unrelieved feelings, suicidal.

(7) General somatic (muscular) (0-4)

This symptom consists of diffuse muscular aching or stiffness, ill-defined and often difficult to locate, but frequently in the back and sometimes in the limbs; these may also feel "heavy". Erratic muscular tone may result in clonic jerks, twitchings, grinding of teeth and an unsteady voice.

" HAVE YOU HAD ANY ACHES OR PAINS DURING THE LAST WEEK? HAVE YOUR LIMBS FELT STIFF, TIGHT, TWITCHY OR JERKY? DOES YOUR VOICE FEEL UNSTEADY, HAVE YOU BEEN GRINDING YOUR TEETH? HOW OFTEN? HOW BAD?

0 = Absent.

1 = Mild. A slight increase in muscular tension, aches and pains, but of no significant concern to the patient.

2 = Moderate. A noticeable increase in symptoms, of concern to the patient but of a sporadic nature and able to be relieved or brought under control by the patient to some extent.

3 = Severe. A significant increase in symptoms being outwith the patient's control and occurring with such severity and regularity (on a daily basis) thereby causing the patient concern and impairment. Periods of total relief from symptoms being very infrequent.

4 = Very severe. Continuous and severe stiffness, pain or clonic jerks. This results in a significant degree of motor impairment and is therefore greatly inhibiting and of much concern to the patient.

(8) General somatic (sensory) (0-4)

Autonomic overactivity may manifest itself as blurring of vision, tinnitus, hot and cold flushes, feelings of weakness, or prickling sensations.

" HAVE YOU SUFFERED FROM ANY OF THE FOLLOWING RECENTLY: RINGING IN YOUR EARS, BLURRED VISION, FLUSHES, PRICKLY SENSATIONS OR FEELING WEAK? HOW OFTEN? HOW BAD? "

0 = Absent.

1 = Mild. One or two definite symptoms of mild intensity occurring once or twice per week, leading to only mild interference with day to day activities.

2 = Moderate. Marked symptoms occurring more than twice per week or continuous milder symptoms present most of the week. Presence of symptoms significantly upsetting daily routine; and while present, impairing daily performance.

3 = Severe. Severe symptoms occurring at least daily or severe sporadic episodes that totally incapacitate while they last. Patient experiences difficulty in getting going and only occasionally experiences respite from symptoms.

4 = Very severe. Patient experiences multiple severe symptoms much of the time or frequent severe sporadic episodes which totally incapacitate, resulting in marked impairment and an inability to perform daily tasks. Patient never totally symptom-free, symptoms only periodically reducing in intensity.

(9) Cardiovascular symptoms (0-4)

Patients may experience cardiovascular irregularities such as tachycardia, and various other arhythmias may be present. Patient may attribute inappropriate degree of significance to minor abnormalities or be fearful of the consequence of such abnormalities.

" HAVE YOU NOTICED RECENTLY ANY OF THE FOLLOWING: INCREASED HEART RATE OR YOUR HEART SEEMING TO RACE OR RUN TOO FAST, PALPITATIONS, PAINS IN YOUR CHEST, THROBBING OF BLOOD VESSELS OF YOUR HEART, FEELING FAINT OR FEELING THAT YOUR HEART MISSES A BEAT? "

0 = Absent.

1 = Mild. An increased awareness of heart rate or heart beat irregularities that do not incapacitate the patient in any way; occurs infrequently, usually not more than three times per week.

2 = Moderate. More persistent tachycardia, arhythmias, angina, palpitations or faintness that are not, according to the patient, under his/her control and are a cause of concern, necessitating an adjustment of the patient's daily routine; occuring frequently almost daily.

3 = Severe. Patient may severely restrict activity for fear of the consequences of tachycardia or irregular cardiac activity and palpitations. Symptoms may be present most of the time.

4 = Very severe. Patient completely preoccupied with cardiovascular symptoms. Severe impairment of function. Symptoms continuously present.

(10) Respiratory symptoms (0-4)

Severe forms of these symptoms may result in hyperventilation and is therefore easy to detect although less severe forms are often less noticeable. The patient may complain of pressure or constriction in chest, choking feelings, sighings, dyspnoea, tightness or gasping for breath.

" HAVE YOU HAD ANY DIFFICULTY IN BREATHING RECENTLY? WHEN? HOW OFTEN? HOW BAD? "

0 = Absent.

1 = Mild. Experience of mild respiratory symptoms, not giving rise to undue concern and not restricting patient's daily activities.

2 = Moderate. A more pronounced loss of regular breathing control necessitating termination of activities in order to regain control of breathing. (less than 5 mins. x2 per day).

3 = Severe. Patient feels he/she is unable to control erratic breathing pattern, unable to regain breathing control and unable to continue any task at hand when breathing pattern becomes disturbed. (greater than 5-10 mins. x4 per day).

4 = Very severe. Frequent and intense respiratory difficulty resulting in prolonged daily episodes of hyperventilation (greater than 30 mins.), and possible concomitant loss of consciousness.

(11) Gastro-intestinal symptoms (0-4)

A great variety of gastro-intestinal symptoms may exist ranging from a very occasional difficulty in swallowing to a medically diagnosed irritable bowel syndrome.

A check list of gastro-intestinal symptoms follows:-

Difficulty in swallowing; wind; dyspepsia; pain before and after meals, burning sensations, fullness, waterbrash, nausea, vomiting, sinking feelings; "working"in abdomen; borborygmi; looseness of bowels; loss of weight; constipation.

" HOW HAS YOUR APPETITE BEEN? HAVE YOU HAD ANY DIFFICULTY IN KEEPING YOUR FOOD DOWN RECENTLY? HAVE YOU BEEN CONSTIPATED RECENTLY OR HAVE YOUR BOWELS BEEN AS REGULAR AS YOU WOULD NORMALLY EXPECT? HAVE YOU HAD HEARTBURN RECENTLY? HAS YOUR STOMACH BEEN TROUBLING YOU AT ALL? HAVE YOU LOST ANY WEIGHT RECENTLY? "

0 = Absent. No major gastro-intestinal upset of any consequence in recent months.

1 = Mild. A minor degree of gastro-intestinal, or bowel irregularity, resulting in a minor degree of irritation and annoyance as opposed to incapacitation.

2 = Moderate. A moderate degree of gastro-intestinal or bowel irregularity, resulting in a degree of incapacitation that is of concern to the patient.

3 = Severe. A severe degree of gastro-intestinal or bowel upset that is often unpredictable and uncontrollable even if food intake is modified, resulting in significant functional impairment.

4 = Very severe. Frequently painful and incapacitating gastro-intestinal or bowel upset, possibly resulting in markedly reduced and modified food intake with concomitant loss of weight. Severe functional impairment.

(12) Genito-urinary symptoms (0-4)

Desire to micturate can reflect intense anxiety. Females may experience various menstrual irregularities, whilst males and females may experience a wide range of sexual dysfunctions. A check list of genito-urinary symptoms follows:-

Frequency of micturition) Urgency of micturition)	in both males and females
Amenorrhea) Menorrhagia)	in females alone
Development of frigidity)	
Ejaculatio praecox) Loss of erection)	in males alone
Impotence)	

Patients need not experience symptoms from all the above categories of symptoms.

" HAS THERE BEEN ANY CHANGE IN THE NUMBER OF TIMES, OR URGENCY WITH WHICH YOU HAVE TO GO TO THE TOILET TO URINATE? HAS THERE BEEN ANY CHANGE IN YOUR LOVE LIFE, SEX LIFE, OR INTEREST IN SEX, RECENTLY? HAS THERE BEEN ANY CHANGE IN THE REGULARITY OF YOUR PERIODS? (FEMALES ONLY). "

0 = Absent.

1 = Mild. A noticeable increase in frequency or urgency of micturition which can be alleviated by partially reducing liquid intake and environmental change and is more of an inconvenience than a handicap. A mild decrease in sexual receptivity/performance/arousal etc. where such dysfunction would not normally be present.

2 = Moderate. A marked increase in urgency or frequency of micturition cannot be brought under control by patient. Sexual dysfunction is evident on many occasions and is therefore of concern to both patient and sexual partner. Females may experience menstrual irregularity which is of concern to them.

3 = Severe. Urgency and frequency of micturition is such that patient organises daily routine around presence and availability of toilets. Sexual dysfunction is evident on most occasions. Marked menstrual irregularity in female patients.

4 = Very severe. Fear of involuntary voiding is such that patient needs to be constantly in reach of a toilet and is therefore severely functionally impaired. Sexual dysfunction is evident on all occasions of attempted sexual intercourse. Female patients are completely amenorrheaic.

(13) Autonomic symptoms (0-4)

Autonomic accompaniments of anxiety may entail any of the following:-

dry mouth; flushing; pallor; tendency to perspire heavily; giddiness; tension headache; raising of hair.

Various combinations of the above check list may be present to a greater or lesser degree.

" HAVE THERE BEEN TIMES RECENTLY WHEN YOU HAVE FELT ANY OF THE FOLLOWING: GIDDY OR UNSTEADY, HAVE SWEATED A LOT, HAD A DRY MOUTH, FELT FAINT, DIZZY, HEADACHES, PIAN AT THE BACK OF THE NECK, BUTTERFLIES. HOW OFTEN? HOW BADLY? "

0 = Absent.

1 = Mild. One or a few of the above symptoms have been present on occasion but were mild and did not cause concern. Present on occasion (not more than twice per week).

2 = Moderate. A number of the above symptoms have been present on a number of occasions causing distress, (greater than twice per week), or a single symptom has been present on a regular basis.

3 = Severe. A number of the above symptoms have been present most of the time, resulting in some impairment to function and marked concern to patient.

4 = Very severe. A number of the above symptoms have been continually present, to the extent that this has markedly impaired the patient carrying out daily routine tasks. Virtually no relief from symptoms.

(14) Behaviour at interview (general) (0-4)

This is not based on the patient's subjective report but is based upon the interviewer's observations of the patient's general appearance and behaviour throughout the whole assessment interview.

Observe general anxiety checklist as follows:-

Tense, not relaxed. Fidgeting: hands, picking fingers, clenching, tics. Restlessness: pacing. Tremor of hands. Furrowed brow. Strained face or voice. Increased muscular tone. Sighing respirations. Facial pallor. Swallowing , belching, sweating. Tremor and eye-lid twitching.

0 = Absent. Calm and relaxed.

1 = Mild. Exhibiting up to two of the above behaviours, occasionally throughout the interview.

2 = Moderate. Intermittently exhibiting two to four of the above behaviours or continually exhibiting up to two of the above behaviours throughout the interview.

3 = Severe. Frequently exhibiting at least four of the above behaviours or continually exhibiting less than four of the above behaviours, resulting in slightly impaired communication.

4 = Very severe. Continually exhibiting the majority of the above behaviours to such an extent that communication is extremely difficult.

APPENDIX 3

KELLNER AND SHEFFIELD SYMPTOM RATING TEST

SELF RATING SCALE

Study number _____

date _____

Describe how you have felt during the PAST WEEK.

If you have not had the symptom at all make a check mark (✓) in the box on the left like this.

	Not at all	A little slightly	A great deal, quite a bit	Extremely, could not have been worse
Headaches or head pains	✓			

If you have had the symptom describe how much it has bothered you or troubled you, for example, like this:

	Not at all	A little slightly	A great deal, quite a bit	Extremely, could not have been worse
Headaches or head pains			✓	

Please answer all questions. Do not think long before answering.

	Not at all	A little slightly	A great deal, quite a bit	Extremely, could not have been worse
1 Feeling dizzy or faint				
2 Feeling tired or lack of energy				
3 Nervous				
4 Feelings of pressure or a tightness in head or body				
5 Scared or frightened				
6 Poor appetite				
7 Heart beating quickly or strongly without reason (throbbing or pounding)				
8 Feeling that there was no hope				
9 Restless or jumpy				
10 Poor memory				

	Self-rating scale			
	Not at all	A little, slightly	A great deal, quite a bit	Extremely, could not have been worse
11 Chest pains or breathing difficulties or feeling of not having enough air				
12 Feeling guilty				
13 Worrying				
14 Muscle pains or aches, or rheumatism				
15 Feeling that people look down on you or think badly of you				
16 Trembling or shaking				
17 Difficulty in thinking clearly or difficulty in making up your mind				
18 Feeling unworthy or a failure				
19 Feeling tense or 'wound up'				
20 Feeling inferior to other people				
21 Parts of body feel numb or tingling				
22 Irritable				
23 Thoughts which you cannot push out of your mind				
24 Lost interest in most things				
25 Unhappy or depressed				
26 Attacks of panic				
27 Parts of your body feeling weak				
28 Cannot concentrate				
29 It takes a long time to fall asleep, or restless sleep or nightmares				
30 Awakening too early and not being able to fall asleep again				

APPENDIX 4

ADVERSE EVENT RECORD AND WITHDRAWAL SYMPTOM CHECKLIST

FVGPRG

AAER

Study No .....

ADVERSE EVENT RECORD

Date of evaluation	Pt. No.....
.....	Initials .....

For the first evaluation please record the adverse events which have occurred during the previous week. For all subsequent evaluations record the adverse events since last evaluation, irrespective of whether you suspect the drug or not.

RECORD HERE concurrent medical illness, injury, or adverse reaction which has been:

- spontaneously reported by patient
- observed by staff
- reported by patient on open questioning, i.e. "How do you feel? Have you felt unwell? Has anything in particular been bothering you"?

RATE SEVERITY of the event using the following scale:

SEVERITY

1 = Mild - Does not hinder the patient's pretreatment functioning, but is an annoyance

2 = Moderate - Definite degree of impairment to functioning, uncomfortable or embarrassing

3 = Severe - Definite hazard to well-being, significant impairment of functioning or incapacitation

9 = Not assessed

ADVERSE EVENT (Print)	SEVERITY	CODE	ACTION TAKEN (Print)

INVESTIGATOR'S SIGNATURE

Study No .....

WITHDRAWAL SYMPTOM CHECK LIST

Current evaluation	Date of evaluation	Pt. No..... Initials .....

INSTRUCTIONS

For the first evaluation please record the symptoms reported to have occurred during the previous week. For all subsequent evaluations describe the symptoms since last evaluation, irrespective of whether you suspect the drug or not.
Check the presence or absence of each symptom on the list as REPORTED BY THE PATIENT ON ACTIVE QUESTIONING, e.g. "Have you had a headache"? "Have you had dry mouth"? etc. If symptom was reported on Adverse Event Record, check the box "REPORTED ON AAER"*.
RATE SEVERITY using the following scale:

SEVERITY

0 = Not present

1 = Mild - Does not hinder the patient's pretreatment functioning, but is an annoyance

2 = Moderate - Definite degree of impairment to functioning, uncomfortable or embarrassing

3 = Severe - Definite hazard to well-being, significant impairment of functioning or incapacitation

9 = Not assessed

SYMPTOM	CODE	REPORTED ON AAER*	SEVERITY	ACTION TAKEN/COMMENTS (Print)
Difficulty getting to sleep				
Disturbed sleep				
Restlessness				
Tremor				
Hyperactivity				
Abdominal cramps				
Sweating a lot				
Convulsions				
Confusion				
Dysphoria				
Anxiety				
Weakness				
Lack of energy				
Numbness				
Loss of appetite				
Nausea				
Apprehension				
Over active				
Headache				
Dizziness				
Faintness				

APPENDIX 5

COPING WITH ANXIETY : A GUIDE TO COGNITIVE THERAPY

COPING WITH ANXIETY: A GUIDE TO COGNITIVE THERAPY

To be human is to have emotional problems. Sometimes we can deal with these problems by ourselves or with the help of family and friends. However, we sometimes also benefit from professional help in overcoming emotional problems before they become so severe as to be disabling.

This booklet is designed to help you make the most of your experience with Cognitive Therapy - a new and generally effective form of treatment for people suffering from anxiety. Read it through several times and discuss anything you're not clear about with your therapist.

SIGNS OF ANXIETY

"What if I fail this exam? My career will be ruined before it starts. I feel so sick just thinking about it that I can't study. But I have to study or . . . .".

"Every time I leave the house I feel sick, I think I'm going to collapse and have to go back home. I can't go anywhere unless someone's with me".

"When I have to talk to strangers I start to sweat and panic - I feel trapped and can't think of anything to say".

"I sometimes feel very tense and uncomfortable, worrying about things that I've got to do the next day, or even the next week or month. I can't seem to get rid of these worrying thoughts no matter how hard I try".

Such are the thoughts and emotions that sweep over those who suffer from anxiety and phobias. Since both anxiety and phobias are rooted in fear, they both indicate the dread of some type of danger or threat to one's wellbeing. This sense of threat is manifested by a wide range of physical symptoms - anxiety's "body language" - which are distressing in themselves; rapid breathing, accelerating heart rate, dizziness, nausea, headache, sweating, dryness of mouth, tightening of throat, pain in various sets of muscles. etc. When the state of anxiety is prolonged - or chronic - these frightening or uncontrollable symptoms may take the form of what seems to be a real disease or disability.

One of the most important facts for a severely anxious person to learn - and to recall to mind at critical moments - is that the symptoms he is experiencing are <u>not</u> dangerous. The racing pulse or pounding heart, the dizziness or nausea, the desire to scream or cry or pound the table - none of these physical or emotional reactions indicate that the person is dangerously ill or "going crazy". They are unpleasant. They are uncomfortable. But they can be tolerated until they go away. And they <u>will</u> go away.

NATURE OF ANXIETY AND PHOBIAS

While phobias cause intense anxiety, accompanied by its various physical and/

and emotional symptoms, the phobic individual is reacting to a specific object or situation which can to some extent and without great inconvenience, be avoided. As long as the feared event, object or situation is not an integral part of the person's life, he can remain free from the anxiety effects of phobia. For instance, someone who has in intense, phobic fear of flying, can usually find ways of getting to places without having to go on an aeroplane.

The anxiety sufferer, however, cannot always pinpoint the source of his anxiety. And even if he can identify the cause, he cannot avoid encountering it; either the demands of his daily life force him to confront the feared circumstances, or he has so completely internalized his fear that the source of it is within himself.

Sometimes it is necessary for a person to experience fear in order to acknowledge the threat of real danger and prepare himself to meet it. A certain degree of anxiety may accompany such fear. But the person who suffers from excessive anxiety or phobic reactions is not responding to the reality of his situation. He may be anticipating a threat to his well-being when there is little likelihood that it will occur. If he is facing a challenge of some sort - an exam, or job interview, he will magnify the difficulties and dwell on the horrors of a negative outcome. At the same time he will underestimate overlook or discount his own ability to cope with whatever he fears. In other words, he misinterprets and distorts reality so that he feels anxious about dangers which either do not exist or which he could cope with effectively if he were not so disabled by his own anxiety reactions.

To make matters worse, when the severely anxious person becomes aware of his own unpleasant physical and emotional reactions, he may begin to dread and fear the symptoms themselves even more than the situation that triggers them. The more upset he gets, the more exaggerated his symptoms become, and he is involved in a self-perpetuating spiral of increasingly intense emotional and physical suffering.

NEW UNDERSTANDING FROM RESEARCH

Since this form of anxiety is based on a misinterpretation of reality, research has revealed that certain thoughts and mental pictures automatically accompany the experience of anxiety. These AUTOMATIC THOUGHTS or cognitions, are usually focussed on the future: "I won't be able to do the job", "I'll lose control of myself and be humiliated", "I'll die from a heart attack", "If I go to the party no-one will talk to me".

The connection between these AUTOMATIC THOUGHTS and the experience of excessive anxiety, suggested to these people studying the problem that if the patient became more aware of those thoughts and changed them to conform with reality, the anxiety would be very much less. Clinical experience with people who suffer from anxiety has shown that this method can be very effective. The approach is called COGNITIVE THERAPY.

COGNITIVE THERAPY IN PRACTICE

In the following anecdote you may recognise the way in which a person's anxious thoughts destroy his ability to function adequately. A lonely young man wants to ask a girl for a date, but every time he has the opportunity to do so the anxious thoughts rise up and he avoids asking her. The 'automatic thoughts' he has are: "She'll think I'm stupid to be so nervous./

nervous. She'll turn me down and I'll look pathetic. I'll have failed yet again."

How would Cognitive Therapy help someone whose anxious thoughts and imaginings interfered with their ability to lead the kind of life that is rewarding to them? First, by helping you to recognise the kind of errors of reasoning in your thinking that cause you to feel upset. Secondly, by helping you to correct these errors and substitute more reasonable and rational thoughts that will not result in excessive, debilitating feelings of nervousness and anxiety. Thirdly, by helping you to understand how your own characteristic ways of looking at the world (what are called UNDERLYING ASSUMPTIONS) may make you vulnerable to thinking in anxiety-provoking ways.

During treatment, your therapist will help you to learn how to challenge your irrational, automatic thoughts and to change maladaptive underlying assumptions. There are a variety of ways of doing this, and your therapist will help you to find the particular ways that help you best. This can be a slow and at times a painful process, and will involve you in taking some risks in 'testing out' your beliefs and ideas to determine how realistic they are. However, the rewards of learning how to control your anxiety will almost certainly compensate more than adequately for the hard work that may be involved. As you gradually eliminate the distortions and inaccuracies in your own thinking you will develop an increasing confidence in your ability to handle situations in your life that previously caused you a lot of difficulty.

STEPS IN COGNITIVE THERAPY

(1) The first step is to recognise your own AUTOMATIC THOUGHTS whenever you feel anxious. In order to help you recognise them, keep these characteristics in mind:

   (a) These thoughts just seem to come out of nowhere, and flash through your mind without you really being aware of them.

   (b) They seem very plausible and reasonable to you at the time you are experiencing them. In fact you accept them as a perfectly reasonable way of thinking in the circumstances, just as you might readily accept the truth of a realistic thought like "The phone is ringing - I must answer it".

   (c) These thoughts are, however, quite unreasonable and irrational as you will realise when you learn to challenge them with reason and facts.

   (d) Automatic thoughts are the kind of thoughts most people would find depressing or anxiety-provoking <u>if</u> they believed them.

(2)/

(2) The second step is to learn how to challenge automatic thoughts with reason and facts about how the world really is. A good way of doing this is to consider all the various thoughts that you might have had instead of the automatic thoughts. When you do this you will begin to realise that the way you thought about the situation was only one of a number of different interpretations. (It is very important to remember that there are always lots of different ways of looking at the same situation). Once you do this you will start to see that the automatic thoughts that caused you to be anxious or upset contained THINKING ERRORS. These errors tend to fall into the following categories:

(a) ALL-OR-NONE THINKING:- Seeing things in black or white rather than in shades of grey (e.g. you're either a total success or a total failure).

(b) OVER-GENERALISING:- Imagining that one bad experience in a situation means that you will always have a bad experience in such situations. (e.g. thinking that you will always be anxious in social situations just because you were extremely anxious at a party you went to recently).

(c) CATASTROPHISING:- Assuming that the worst possible thing is bound to happen in a situation that you find difficult (e.g. after an argument with your boss, assuming that you'll probably lose your job, have to sell your house, and won't ever be able to work again).

(d) EXAGGERATING:- Blowing things up out of proportion. Reaction to a situation that is difficult or embarassing or irritating or upsetting, as if it were a major disaster, (e.g. being extremely upset when a neighbour you know slightly criticizes the behaviour of a friend of yours).

(e) IGNORING THE POSITIVE:- Overlooking positive experiences and positive aspects of a situation because they 'don't count' for some reason. Dwelling exclusively on the negative aspects of a situation (e.g. thinking only of all your negative qualities and personal failings after you have been turned down for a job).

(f) JUMPING TO CONCLUSIONS:- Coming to a quite arbitrary conclusion about something in the absence of any definite facts to justify this, (e.g. deciding that your new neighbour doesn't like you just because she turned down your invitation to go to the local supermarket with her).

(g) 'SHOULD'STATEMENTS:- This refers to automatic thoughts that cause excessive anxiety or guilt because they inappropriately contain the words 'should' or 'must' or 'always' or 'never'. People generally have these thoughts when they try to live by personal rules or standards that may in fact be excessively rigid and overdemanding and have no real application to normal, everyday life, (e.g. I must always look my best or people won't like me).

(3) Once you have learnt to identify your automatic thoughts and the thinking errors they contain, the third step is to practice substituting RATIONAL RESPONSES/

RESPONSES for the automatic thoughts. Thus, instead of automatically responding to the situation with a series of negative, anxiety-provoking thoughts, you will gradually learn to respond to situations in more reasonable ways. For example: you will begin to realise that the experience of acute anxiety is always limited in time and that you can learn to control anxiety by not over-reacting to the symptoms. You will also learn to test out your anxious thoughts and beliefs about what might happen to you in certain situations, by conducting PERSONAL EXPERIMENTS. It very often happens that people are not as anxious as they imagined they would be in certain situations. Remember that in nearly all anxiety-provoking situations there are what we call RESCUE FACTORS: these are things that make the feared consequences of being anxious tolerable, unlikely to happen, limited in time, etc.

(4) When you have practised going through the first three steps and learnt how to control,your anxiety symptoms in your everyday life, the fourth stage is to modify any UNDERLYING ASSUMPTIONS you may have that make you vulnerable to being anxious. These are a little more difficult to explain than automatic thoughts; they refer to the characteristic ways in which you look at the world and think about yourself. For example anxious people very often have excessive needs for love and approval from other people, or beliefs that always being very successful at work is of vital importance to being a worthwhile person. They may have expectations of life that are very unlikely to be satisfied or perhaps excessive feelings of responsibility for other people. As therapy progresses you will begin to learn about the kind of beliefs and assumptions that you have that may make you vulnerable to further episodes of anxiety in the future. Once these are identified you can work with your therapist to try to change them so that you are less likely to experience any recurrence of anxious thoughts and feelings.

The following statements are examples of maladaptive underlying assumptions:

(a) In order to be happy I have to be successful in everything I do.

(b) I must be liked by people at all times.

(c) If I make a mistake it means I'm incompetent.

(d) I can't live without being loved.

(e) If somebody disagrees with me it must mean he doesn't like me.

(f) My value as a person mainly depends on what other people think of me.

GENERAL COMMENT ABOUT COGNITIVE THERAPY

(1) This type of therapy works best where there is a close working relationship between you and your therapist. This relationship should be a collaborative one in which you both work together as a team. It should be an open relationship in which you feel comfortable talking about any doubts or anxieties that you may have about your progress, your personal life, or the way in which your therapist behaves.

(2)/

(2) Throughout therapy you will be given HOMEWORK to do between therapy sessions. This is a very important part of Cognitive Therapy and it is important that you understand both what you have to do, and why. It will almost certainly be useful to have a notebook and pen handy during therapy sessions so that you can take a note of anything you need to remember.

(3) During your first few sessions of therapy, as part of the general assessment of your problems and present circumstances, it will be useful to set certain TREATMENT GOALS. Setting goals gives impetus to the process of treatment. If you have in your mind a clear picture of how you would like to change and what you imagine your life would be like if you were free of anxiety, you will know what you are working toward. So share your ideas with your therapist so that he can help you reach your goal.

(4) In addition to the steps in Cognitive Therapy outlined above, there may well be other therapeutic techniques and approaches that you can use to learn how to control your anxiety, or to put yourself in situations that you have been afraid of, or to learn more effective ways of behaving in social situations. For example, your therapist may help you learn how to relax, or how to approach fearful situations using a method called 'graded exposure', or how to become more assertive using 'role-playing' techniques. It is not always clear at the start of treatment which approach is most likely to be of most benefit to you, and finding the right approach may involve some degree of trial and error.

CONCLUDING COMMENTS

This booklet has hopefully given you some idea of what is involved in Cognitive Therapy. Remember that the purpose of this type of treatment is to teach you skills that you can carry on using once therapy has ended. Learning to be confident about overcoming anxiety symptoms may take quite a while. It is something that you will probably need to work at on your own whenever you come across situations in life that are stressful or problematic in some way. No-one's life is ever completely free of anxiety or depression - the important goal is to relieve yourself of excessive anxiety that inhibits your ability to enjoy life and realise your potential. Learning how to do this is never a smooth, straight-forward process - you are bound to have some ups and downs and occasional setbacks. The important thing is that with hard work and practice you will gradually become more and more confident about doing things without anxiety that you had previously thought were quite out of reach.

ACKNOWLEDGEMENT

This booklet is based on a similar one described in Beck, A.T. and Emery,G. "Cognitive Therapy of Anxiety and Phobic Disorders". Unpublished treatment manual, 1979.

c. Robert Durham, Principal Clinical Psychologist,
Royal Dundee Liff Hospital

DAILY RECORD OF DYSFUNCTIONAL THOUGHTS

DATE	SITUATION Describe: 1. Actual event leading to unpleasant emotion, or 2. Straem of thoughts, daydream, or recollection, leading to unpleasant emotion.	EMOTION(S) 1. Specify sad/anxious/ angry etc. 2. Rate degree of emotion, 1 - 100	AUTOMATIC THOUGHT(S) 1. Write automatic thought(s) that preceded emotion(s). 2. Rate belief in automatic thought(s), 0 - 100%.	RATIONAL RESPONSE 1. Write rational response to automatic thought(s). 2. Rate belief in rational response, 0 - 100%.	OUTCOME 1. Re-rate belief in automatic thought(s) 0 - 100 2. Specify and rate subsequent emotions 0 - 100

EXPLANATION: When you experience an unpleasant emotion, note the situation that seemed to stimulate the emotion. (If the emotion occurred while you were thinking, daydreaming,etc., please note this). Then note the automatic thought associated with the emotion. Record the degree to which you believe this thought: 0% = not at all; 100% = completely. In rating degree of emotion: 1 = a trace; 100 = the most intense possible.

APPENDIX 6

GENERAL HEALTH QUESTIONNAIRE

Study Number ..... Date .....

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, over the past few weeks. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

HAVE YOU RECENTLY:

1.	Been feeling perfectly well and in good health?	Better than usual	Same as usual	Worse than usual	Much worse than usual
2.	Been feeling in need of a good tonic?	Not at all	No more than usual	Rather more than usual	Much more than usual
3.	Been feeling run down and out of sorts?	Not at all	No more than usual	Rather more than usual	Much more than usual
4.	Felt that you are ill?	Not at all	No more than usual	Rather more than usual	Much more than usual
5.	Been getting any pains in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
6.	Been getting a feeling of tightness or pressure in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
7.	Been able to concentrate on whatever you are doing?	Better than usual	Same as usual	Less than usual	Much less than usual
8.	Been afraid that you were going to collapse in a public place?	Not at all	No more than usual	Rather more than usual	Much more than usual
9.	Been having hot or cold spells?	Not at all	No more than usual	Rather more than usual	Much more than usual
10.	Been perspiring (sweating) a lot?	Not at all	No more than usual	Rather more than usual	Much more than usual
11.	Found yourself waking early and unable to get back to sleep?	Not at all	No more than usual	Rather more than usual	Much more than usual
12.	Been getting up feeling your sleep has not refreshed you?	Not at all	No more than usual	Rather more than usual	Much more than usual
13.	Been feeling to tired and exhausted even to eat?	Not at all	No more than usual	Rather more than usual	Much more than usual
14.	Lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
15.	Been feeling mentally alert and wide awake?	Better than usual	Same as usual	Less alert than usual	Much less alert

16./

16.	-been feeling full of energy?	Better than usual	Same as usual	Less energy than usual	Much less energetic
17.	-had difficulty in getting off to sleep ?	Not at all	No more than usual	Rather more than usual	Much more than usual
18.	-had difficulty in staying asleep once you are off?	Not at all	No more than usual	Rather more than usual	Much more than usual
19.	-been having frightening or unpleasant dreams?	Not at all	No more than usual	Rather more than usual	Much more than usual
20.	-been having restless, disturbed nights?	Not at all	No more than usual	Rather more than usual	Much more than usual
21.	-been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
22.	-been taking longer over the things you do?	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
23.	-tended to lose interest in your ordinary activities?	Not at all	No more than usual	Rather more than usual	Much more than usual
24.	-been losing interest in your personal appearance?	Not at all	No more than usual	Rather more than usual	Much more than usual
25.	-been taking less trouble with your clothes?	More trouble	About same	Less trouble	Much less
26.	-been getting out of the house as much as usual?	More than usual	Same as usual	Less than usual	Much less than usual
27.	-been managing as well as most people would in your shoes?	Better than most	About the same	Rather less well	Much less well
28.	-felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well
29.	-been late getting to work, or getting started on your housework?	Not at all	No later than usual	Rather later than usual	Much later than usual
30.	-been satisfied with the way you've carried out your task?	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
31.	-been able to feel warmth and affection for those near to you?	Better than usual	About same as usual	Less well than usual	Much less well
32.	-been finding it easy to get on with other people?	Better than usual	About same as usual	Less well than usual	Much less well
33.	-spent much time chatting with people?	More time than usual	About same as usual	Less than usual	Much less than usual
34.	-kept feeling afraid to say anything to people in case you made a fool of yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual

35./

35.	-felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
36.	-felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
37.	-felt you're just not able to make a start on anything?	Not at all	No more than usual	Rather more than usual	Much more than usual
38.	-felt yourself dreading everything that you have to do?	Not at all	No more than usual	Rather more than usual	Much more than usual
39.	-felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
40.	-felt you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much more than usual
41.	-been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
42.	-been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
43.	-been taking things hard?	Not at all	No more than usual	Rather more than usual	Much more than usual
44.	-been getting edgy and bad-tempered?	Not at all	No more than usual	Rather more than usual	Much more than usual
45.	-been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
46.	-been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much less able
47.	-found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
48.	-had the feeling that people were looking at you?	Not at all	No more than usual	Rather more than usual	Much more than usual
49.	-been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much more than usual
50.	-been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
51.	-been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
52.	-felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
53.	-been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much less hopeful
54.	-been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much less than usual

55.

55.	-been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
56.	-felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual
57.	Thought of the possibility that you might make away with yourself?	Definitely not	I don't think so	Has crossed my mind	Definitely have
58.	Found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual
59.	Found yourself wishing you were dead and away from it all?	Not at all	No more than usual	Rather more than usual	Much more than usual
60.	Found that the idea of taking your own life kept coming into you mind?	Definitely Not	I don't think so	Has crossed my mind	Definitely has

APPENDIX 7

'TENSE - RELAXED' VISUAL ANALOGUE

APPENDIX 8

'TARGET - SYMPTOM' VISUAL ANALOGUE

At this / the first visit you mentioned that .....particularly bothered you. Could you show how much it bothered you over the past week by marking clearly and at right angles across the line below.

Not at all ⊢----------⊣ Extremely bad, could not be worse.

APPENDIX 9

LETTER OF INVITATION

Dear

Benzodiazepines (Tranquillizers, Sleeping Tablets)

As you may be aware, there is growing concern over the longer term use of certain medicines. The benzodiazepines have been in use now for 25 years. It has become increasingly clear that whilst they were a great advance on what was available before, they are not free from problems. One such problem is that some patients find it difficult to cope without them, but do not feel them to be very helpful either.

We are reviewing the use of these medicines, and would like you to attend an appointment to discuss your treatment with benzodiazepines. We are not suggesting that you stop your medication at present.

Your appointment is on ..... at .....
at .....
and will be with .....
It will take approximately 40 minutes.

Please let us know whether you will be able to keep this appointment by phoning Mrs Swanson, at the University of Stirling (tel Stirling 73171, extension 2082) between 9.30 am and 12.30 pm any weekday. If this time is not suitable for you, please phone the above number to arrange an alternative appointment.

Thank you very much for your help.

Yours sincerely,

APPENDIX 10

BECK DEPRESSION INVENTORY

BECK INVENTORY

Name: . . . . . Date: . . . . . .

On this questionnaire are groups of statements. Please read each group of statements carefully, then pick out the one statement in each group which best describes the way you have been feeling during the past week, including to-day. Circle the number beside the statement you picked. Please be sure to read all the statements in each group before making your choice.

1. 0 I do not feel sad
   1 I feel sad
   2 I am sad all the time and I can't snap out of it
   3 I am so sad or unhappy that I can't stand it

2. 0 I am not particularly discouraged about the future
   1 I feel discouraged about the future
   2 I feel I have nothing to look forward to
   3 I feel that the future is hopeless and that things cannot improve

3. 0 I do not feel like a failure
   1 I feel I have failed more than the average person
   2 As I look back on my life, all I can see is a lot of failures
   3 I feel I am a complete failure as a person

4. 0 I get as much satisfaction out of things as I used to
   1 I don't enjoy things the way I used to
   2 I don't get real satisfaction out of anything anymore
   3 I am dissatisfied or bored with everything

5. 0 I don't feel particularly guilty
   1 I feel guilty a good part of the time
   2 I feel quite guilty most of the time
   3 I feel guilty all of the time

6. 0 I don't feel I am being punished
   1 I feel I may be punished
   2 I expect to be punished
   3 I feel I am being punished

7. 0 I don't feel disappointed in myself
   1 I am disappointed in myself
   2 I am disgusted with myself
   3 I hate myself

8. 0 I don't feel I am any worse than anybody else
   1 I am critical of myself for my weakness or mistakes
   2 I blame myself all the time for my faults
   3 I blame myself for everything bad that happens

9. 0 I don't have any thoughts of killing myself
   1 I have thoughts of killing myself, but I would not carry them out
   2 I would like to kill myself
   3 I would kill myself if I had the chance

10. 0 I don't cry any more than usual
    1 I cry more now than I used to
    2 I cry all the time now
    3 I used to be able to cry, but now I can't cry even though I want to

11. 0 I am no more irritated now than I ever was
    1 I get annoyed or irritated more easily than I used to
    2 I feel irritated all the time now
    3 I don't get irritated at all by the things that used to irritate me

12. 0 I have not lost interest in other people
    1 I am less interested in other people than I used to be
    2 I have lost most of my interest in other people
    3 I have lost all of my interest in other people

/P.T.O.

13 0 I make decisions about as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty in making decisions than I used to
3 I can't make decisions at all anymore

14. 0 I don't feel I look any worse than I used to
1 I am worried that I am looking old or unattractive
2 I feel that there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly

15. 0 I can work about as well as before
1 It takes an extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can't do any work at all

16 0 I can sleep as well as usual
1 I don't sleep as well as I used to
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

17. 0 I don't get more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything

18 0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all anymore

19. 0 I haven't lost much weight, if any, lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds
I am purposely trying to lose weight by eating less. Yes .... No ....

20. 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains, or upset stomach, or constipation
2 I am very worried about physical problems and it is hard to think of much else
3 I am so worried about my physical problems, that I cannot think about anything else

21. 0 I have not noticed any recent change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

APPENDIX 11

SOCIAL PROBLEMS QUESTIONNAIRE

Name .....

SOCIAL QUESTIONNAIRE

Please underline the most appropriate answer.

A. Housing (EVERYONE ANSWER)

1. Are your housing conditions adequate for you and your family's needs ?	Adequate	Slightly inadequate	Markedly inadequate	Severely inadequate
2. How satisfied are you with your present accommodation ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

B.Work (FOR ALL MEN AND WOMEN WORKING OUTSIDE THE HOME)
Tick box if not applicable ☐

3. How satisfied are you with your present job ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied
4. Do you have problems getting on with any of the people at your work ?	No problems	Slight problems	Marked problems	Severe problems

(FOR HOUSEWIVES WITH NO OUTSIDE WORK)
Tick box if not applicable ☐

5. How satisfied are you with being a housewife ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

(FOR HOUSEWIVES WITH A FULL OR PART-TIME JOB OUTSIDE THE HOME)
Tick box if not applicable ☐

6. How satisfied are you with working and running a home ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

(FOR THOSE WHO ARE NOT WORKING - RETIRED, UNEMPLOYED OR OFF SICK)
Tick box if not applicable ☐

7. How satisfied are you with this situation ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

C. Financial Circumstances (EVERYONE ANSWER)

8. Is the money coming in adequate for you and your family's needs ?	Adequate	Slightly inadequate	Markedly inadequate	Severely inadequate

Please turn over .....

SOCIAL QUESTIONNAIRE (2)

9. Do you have any difficulties in meeting bills and other financial commitments ?	No difficulties	Slight difficulties	Marked difficulties	Severe difficulties
10. How satisfied are you with your financial position ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

D. Social Contacts (EVERYONE ANSWER)

11. How satisfied are you with the amount of time you are able to go out ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied
12. Do you have any problems with your neighbours ?	No problems	Slight problems	Marked problems	Severe problems
13. Do you have any problems getting on with any of your friends ?	No problems	Slight problems	Marked problems	Severe problems
14. How satisfied are you with the amount of time you see your friends ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied
15. Do you have any problems getting on with any close relative ? (include parents, in-laws, or grown-up children)	No problems	Slight problems	Marked problems	Severe problems
16. How satisfied are you with the amount of time you see your relatives ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

E. Marriage and boyfriends / girlfriends

17. What is your marital status ?	Single	Married / cohabiting	Widowed	Separated	Divorced

(FOR ALL THOSE WHO ARE MARRIED OR HAVE A STEADY RELATIONSHIP)

Tick box if not applicable ☐

18. Do you have difficulty confiding in your partner ?	No difficulty	Slight difficulty	Marked difficulty	Severe difficulty

Please turn over .....

SOCIAL QUESTIONNAIRE (3)

19. Are there any sexual problems in your relationship ?	No problems	Slight problems	Marked problems	Severe problems
20. Do you have any other problems getting on together ?	No problems	Slight problems	Marked problems	Severe problems
21. How satisfied in general are you with your relationship ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied
22. Have you recently been so dissatisfied that you have considered separating from your partner ?	No	Sometimes	Often	Yes, planned or recent separation

(FOR ALL THOSE WHO ARE NOT MARRIED / DO NOT HAVE A STEADY RELATIONSHIP)

Tick box if not applicable ☐

23. How satisfied are you with this situation ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

F. Domestic Life (FOR THOSE WITH CHILDREN UNDER 18)

Tick box if not applicable ☐

24. Do you have any difficulties coping with your children ?	No difficulties	Slight difficulties	Marked difficulties	Severe difficulties
25. How satisfied do you feel with your relationship with the children ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

(FOR THOSE WITH CHILDREN OF SCHOOL AGE)

Tick box if not applicable ☐

26. Are there any problems involving your children at school ?	No problems	Slight problems	Marked problems	Severe problems

(FOR ALL THOSE WITH OTHER ADULTS LIVING WITH THEM - INCLUDING RELATIVES BUT EXCLUDING SPOUSE)

Tick box if not applicable ☐

27. Do you have any problems about sharing household tasks ?	No problems	Slight problems	Marked problems	Severe problems

Please turn over .....

28. Do you have any difficulties with the other adults in your household ?	No difficulties	Slight difficulties	Marked difficulties	Severe difficulties
29. How satisfied are you with this arrangement ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

G. Legal Matters (EVERYONE ANSWER)

30. Do you have any legal problems (custody, maintenance, compensation etc.) ?	No problems	Slight problems	Marked problems	Severe problems

H. For Those who are Living Alone

Tick box if not applicable ☐

31. Do you have any difficulties living and managing on your own ?	No difficulties	Slight difficulties	Marked difficulties	Severe difficulties
32. How satisfied are you with living on your own ?	Satisfied	Slightly dissatisfied	Markedly dissatisfied	Severely dissatisfied

I. Other (EVERYONE ANSWER)

33. Do you have any other social problems or problems ?	No problems	Slight problems	Marked problems	Severe problems

If so please specify .....

.....

.....

APPENDIX 12

BENZODIAZEPINE DEPENDENCY QUESTIONNAIRE

Name .....

Benzodiazepine Study : Patient Questionnaire

Please circle the most suitable reply to the following questions :-

1. How important is your medication in helping you cope ?

Not important	A little important	Very important	Vital / essential

2. Does being on your medication concern you at all ?

Not concerned at all	A little concerned	Definitely concerned	Very much concerned/worried

3. How easy do you think it would be for you to stop your medication ?

Very easy	Fairly easy	Fairly difficult	Very difficult

4. What do you think about your current medication dosage ?

Extremely high	A little	Just about right	Extremely low

5. How willing would you be to stop your medication ?

Very willing	Fairly willing	Fairly unwilling	Very unwilling

6. How do you think you would feel if your medication was changed ?

Not concerned at all	A little concerned	Definitely concerned	Very much concerned / worried

7. How do you think you would feel if your medication was stopped ?

Not concerned at all	A little concerned	Definitely concerned	Very much concerned / worried

-felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
-felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
-felt you're just not able to make a start on anything?	Not at all	No more than usual	Rather more than usual	Much more than usual
-felt yourself dreading everything that you have to do?	Not at all	No more than usual	Rather more than usual	Much more than usual
-felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
-felt you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
-been taking things hard?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been getting edgy and bad-tempered?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much less able
-found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
-had the feeling that people were looking at you?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
-felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
-been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much less hopeful
-been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much less than usual