THE PSYCHOLOGICAL AND PHARMACOLOGICAL TREATMENT OF PANIC DISORDER AND AGORAPHOBIA IN PRIMARY CARE

DONALD MACFIE SHARP M.A., M.Sc.

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Department of Psychology
University of Stirling
Scotland.

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For Wendy and Calum,
in memory of Lovat.

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ABSTRACT

Following a review of treatment outcome study methodology, a comparative study of psychological versus pharmacological treatments was conducted; subsidiary studies investigated aspects of treatment outcome in more detail.

193 patients with DSM III-R panic disorder with or without agoraphobia were randomly allocated to; fluvoxamine, placebo, fluvoxamine + CBT (cognitive behaviour therapy), placebo + CBT, or CBT alone. Patients received no concurrent treatments and were treated to the same schedule, with therapist contact balanced across groups. Treatments were conducted in the primary care setting. Outcome at treatment end-point and 6 month follow-up, assessed in terms of both statistical and clinical significance, showed patients receiving active treatments improved significantly, with improvement better preserved over follow-up in the groups receiving CBT. The CBT alone and fluvoxamine + CBT groups showed the most consistent gains, the latter group showing gains earliest in treatment. Outcome was also investigated using brief global ratings of symptom severity, change in symptoms following treatment, general wellbeing and social disruption, completed by psychologist, referring GPs, and patients. Using these measures all active treatments showed statistical advantage over placebo with the groups employing CBT showing the most robust and consistent response. Overall there were no significant differences in drop-out rates between groups although the drop-out rate for patients receiving CBT alone was higher than that for placebo + CBT. Agreement with main outcome measures was demonstrated for psychologist and patient ratings, but not for GP ratings. An investigation of panic attack variables as treatment outcome measures indicated that these did not function as discriminative treatment outcome measures with all treatment groups showing significant reductions in panic attack variables over treatment with few significant differences between treatment groups on any variable throughout treatment. An investigation of prognostic indicators of treatment outcome indicated good prediction of post treatment response using pre-treatment measures of anxiety level, frequency of panic attacks, extroversion and treatment group. Predictions of outcome at 6 month follow-up were less robust. Results are discussed in terms of their relevance to wider clinical practice.

CHAPTER 1 INTRODUCTION AND HISTORICAL PERSPECTIVE

1.1 Introduction

Panic, the sudden onset of overwhelming physical and psychological symptoms coupled with feelings of fear, terror or extreme discomfort has long been recognised as part of human emotional experience. The term panic is deeply entrenched in our cultural mythology being named after the ancient Greek god Pan, the god of nature. Pan lived in the countryside where he presided over the flora and fauna (Smith 1872). Mythology has it that Pan would sleep in thickets or caves near the roadside, and if disturbed from his sleep by passers-by would, from his hiding place, emit a blood-curdling scream terrorising those who heard it. "Hence sudden fright without any visible cause was ascribed to Pan, and was called a Panic fear." (Smith 1872 p518). Whilst the origins of the term may have faded into the myths from which they arose, panic remains a current and ubiquitous emotional descriptor. In everyday terms we "panic" in a range of situations, from failing to meet a deadline, to being faced with immediate life-threatening danger. Such ubiquity might suggest that the term panic has little practical or clinical utility, being all things to all men. On the contrary, many have argued that panic, or more accurately panic attacks, are a definable, recognisable and common clinical occurrence giving rise, particularly in the past 15-20 years, to a substantial clinical literature (Rachman & Maser 1988, Barlow 1988, Baker 1989, McNally 1994, Wolfe & Maser 1994). The following thesis will describe the clinical phenomenon of panic attacks, their high prevalence, and given the latter, necessary treatment strategies. The thesis will focus on treatment outcome research in panic disorder with particular attention being paid to the methodological adequacy of treatment outcome research. Treatment outcome studies designed to address methodological shortcomings in previous research will be described, and the relevance of findings to wider clinical practice discussed.

1.2 Historical Perspective

The origins of the concept of panic in ancient mythology have been described. The construct also has a considerable clinical history. Freud coined the term "anxiety attacks" for what he described as "spontaneous anxiety attacks which take the form of vertigo, palpitation, dyspnoea, trembling, sweating, and so on." (Freud 1895/1962, p133). He noted that these attacks can erupt into consciousness without

apparently being triggered by any antecedent thoughts whilst commonly being accompanied by fears of impending death or insanity. Freud also presaged much later psychological discussion in noting that "...in the case of agoraphobia, etc., we often find the recollection of an anxiety attack; and what the patient actually fears is the occurrence of such an attack under the special conditions in which he believes he cannot escape it." (Freud 1985/1962, p81). Similar descriptions of agoraphobia as resulting from a fear of untoward physical sensations were encapsulated in the contemporary theories of Benedikt (1870) and Westphal (1871) and described under the terms Platzschwindel (dizziness occurring in open spaces) and Platzangst (fear of open spaces). It has been argued (Barlow 1988, McNally 1994) that much of the clarity of Freud's original thinking on the phenomenology of panic was lost with the development of his ideas of sexual aetiology and psychodynamic treatment. Nonetheless, all of the theories described above recognise the central notion of distressing sudden attacks involving physiological disruption, with emotional and behavioural change occurring subsequent to them. As such they can be seen as the foundation on which many current notions of panic disorder rest.

Ideas on panic attacks were not restricted to the field of psychopathology, with descriptions of similar phenomena provided in the medical literature. Such accounts were often given by physicians working in situations where people experienced intense threat or stress, thus the history of the construct of panic runs as a thread through the recent history of medical practice in warfare. For example, the physician De Costa described a syndrome he encountered in a series of 300 patients seen during the American Civil War (De Costa 1871). The syndrome was characterised by dizziness, palpitations and unexplained distress that arose without any clear or obvious cause. Relying on his training as a physician De Costa labelled these phenomena "irritable heart" or "irritable heart of the soldier". The Great War of 1914-1918 also gave rise to further descriptions of similar events. Lewis (1917) described a collection of symptoms similar to those noted by De Costa. Noting that these symptoms occurred amongst battle weary soldiers especially on physical exertion associated with combat activities Lewis coined the term "effort syndrome". In an early reference to the relevance of stress and personality as precipitants for the condition, Lewis emphasised the importance of individual physical and psychological constitution and the relevance of continuous exposure to battle. At the same time,

with regard to seemingly the same syndrome Oppenheim and colleagues coined the term "neurocirculatory asthenia", (Oppenheim et al 1918). This subsequently became a term commonly applied to anxiety states with marked cardiovascular features (Cohen & White 1950). Cohen & White (1950) also list other labels that have been employed for similar collections of symptoms. These include, "vasoregulatory asthenia", "nervous tachycardia", "vasomotor neurosis", and "nervous exhaustion", (Cohen & White 1950). All of these clinical syndromes share features in common with the present day understanding of panic attacks. They are not, however, described with sufficient scientific accuracy to allow the conclusion that they are relevant only to panic attacks. Indeed some of these descriptions have been included in historical perspectives on other anxiety disorders, in particular Generalised Anxiety Disorder. It is also likely, given the war setting of many of these descriptions that there will be considerable overlap with what is now classified as Post-Traumatic Stress Disorder. Some evidence for the existence of a panic-based disorder as distinct from other forms of anxiety was provided in the work of Roth (Roth 1959, 1960). In analysing data on 135 patients, Roth (1959) identified a syndrome, which he argued was separate from what he termed anxiety neurosis. This "phobic anxiety-depersonalisation syndrome" was characterised by attacks similar to panic attacks in which the phenomenon of depersonalisation was suggested to be a major factor. These patients were also suggested to develop agoraphobic avoidance secondary to these attacks. One of the most important features of Roth's work was the differentiation of this syndrome from other anxiety disorders. At the same time that Roth was conducting his studies further evidence of the distinct nature of panic attacks was emerging from work on patients response to pharmacological treatment. With this work Donald Klein (Klein & Fink 1962, Klein 1964, Klein 1981) is popularly credited with recognising the relevance of panic attacks in the psychopathology of anxiety disorders and beginning the more recent scientific study of the phenomenon. In the late 1950s Klein was studying the effects and treatment efficacy of the then experimental drug, imipramine, which was synthesised by small changes to the chemical structure of the major tranquilliser chlorpromazine. It was assumed that this new drug would be effective in the treatment of schizophrenia. Klein and colleagues used imipramine to treat a group of highly anxious in-patients labelled as "schizophrenic" but who nonetheless had neither delusions nor

hallucinations and who had previously failed to respond to chlorpromazine. Following the open clinical trial (Klein & Fink 1962), the patients reported that they continued to experience their chronic anxiety unabated. Their therapists were in agreement with the patients assessment of their condition. Nursing staff, however, reported a significant change in the patients. Prior to starting on imipramine the patients would rush to the nursing station repeatedly claiming they were about to die and expressing considerable terror. The patients would respond to comfort from nursing staff and the terror would eventually pass. During treatment with imipramine this behaviour stopped and patients became apparently more able to move around the hospital unaccompanied. Klein reported this finding (Klein & Fink 1962) and conducted a further small placebo controlled trial of 14 similar patients of whom 6 received placebo, 7 received imipramine, and 1 received chlorpromazine (Klein 1964). This more controlled study produced similar findings with the patients receiving imipramine showing the same pattern of improvement. It appeared therefor that treatment response to imipramine differentiated between two forms of anxiety. The sudden-onset episodes of terror which Klein identified as panic attacks were responsive to the drug, whilst the more chronic anxiety which Klein suggested was anticipatory anxiety secondary to the panic attacks did not. This "pharmacological dissection" (Klein 1981) of panic attacks as a form of anxiety qualitatively distinct from anticipatory, or chronic general anxiety is the central feature of Klein's reasoning and represents the modern beginning of the study of panic attacks as a disorder in it's own right. Klein's observations of the response to imipramine led him not only to distinguish between panic attacks and other forms of anxiety, but also to view agoraphobia as a secondary complication of panic attacks (Klein 1981, Klein & Klein 1989). For Klein, people with agoraphobia were not afraid of crowded or public places per se, indeed he observed that they were often able to enter such places if accompanied by trusted companions, rather they feared the occurrence of panic attacks in those or similar situations where escape might be difficult or embarrassing.

It is clear that the notion of panic or panic attacks has a considerable history. It is only relatively recently, through the work of Roth and Klein that panic attacks came to be regarded as a clinical phenomenon in their own right distinguished from

anticipatory and general anxiety and with particular consequences as seen in the development of agoraphobic avoidance.

1.3 Classification

Western psychiatry has developed two main classification systems in order to identify and collate clinically observed symptom groupings.

The first of these is the World Health Organisation sponsored International Classification of Diseases, now in it's tenth revision (ICD 10, WHO 1992). The ICD system is not a diagnostic manual but a less descriptive compendium developed to aid the gathering of statistical information on morbidity and mortality (Lipshitz 1988). The diagnoses contained in the ICD system are guides for classification rather than a set of operationalised rules by which a definitive classification can be achieved. These limitations mean that categories employed in the ICD system are overinclusive and too ambiguous for it to function as a clinically useful diagnostic system (Jablensky 1985).

A more clinically useful diagnostic system is provided by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM). This system provides detailed criteria against which symptomatology can be assessed for each diagnostic category and specifies inclusion and exclusion criteria thus permitting operationalised research classifications. The Diagnostic and Statistical Manual of Mental Disorders has been adopted as an international standard in research classification.

The development of present day concepts of anxiety can be traced through the development of the DSM. Early versions of the manual, DSM I (1952) and DSM II (1968), reflected the theoretical zeitgeist by adopting a predominantly psychodynamic perspective, classifying the anxiety disorders under the heading of neuroses. In DSM III (1980), however, the anxiety disorders emerged as a category in their own right with the term "neuroses" being retained only as a parenthetic subcategory. In contrast to the previous DSM I & II systems, DSM III takes an atheoretical stance holding no implications for aetiology, and also includes somatic aspects of anxiety in classifying disorders, which were not discussed in DSM I or DSM II. In DSM III the anxiety disorders are classified in two groups, the Phobic

Disorders (or phobic neuroses), and the Anxiety States (or anxiety neuroses). The classifications permissible under each category are given in Table 1.1.

Table 1.1. Anxiety Disorders: Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association

DSM III (1980)	DSM III-R (1987)	DSM IV (1994)
ANXIETY DISORDERS	ANXIETY DISORDERS (OR ANXIETY AND PHOBIC NEUROSES	ANXIETY DISORDERS
Phobic Disorders (or Phobic Neuroses)		
		Panic Disorder Without Agoraphobia
Agoraphobia with panic attacks	Panic Disorder	
Agoraphobia without panic attacks	Panic Disorder With Agoraphobia	Panic Disorder With Agoraphobia
Social phobia	Agoraphobia Without History of Panic Disorder	Agoraphobia Without History of Panic Disorder
Simple phobia	Social Phobia	Specific Phobia
Anxiety State (or Anxiety Neuroses)	Simple Phobia	Social Phobia
Panic Disorder	Obsessive-Compulsive Disorder	Obsessive-Compulsive Disorder
Generalised Anxiety Disorder	Post-Traumatic Stress Disorder	Post-Traumatic Stress Disorder
Obsessive-Compulsive Disorder (or Obsessive-Compulsive Neurosis)	Generalised Anxiety Disorder	Acute Stress Disorder
	Anxiety Disorder Not Otherwise Specified	Generalised Anxiety Disorder
Post-Traumatic Stress Disorder		Anxiety Disorder Due to General Medical Condition/Substance Abuse
Atypical Anxiety Disorder		
		Anxiety Disorder Not Otherwise Specified

Panic Disorder was recognised as a discrete psychiatric entity for the fist time in DSM III. A panic attack was defined as an episode of sudden onset intense apprehension, fear or terror occurring in circumstances other than during marked physical exertion or in a life-threatening situation. The attacks should not be precipitated only by exposure to a circumscribed phobic stimulus. A panic attack comprised at least four of a list of twelve physical symptoms namely, dyspnoea, palpitations, chest pain or discomfort, choking sensations, dizziness, unreality feelings, tingling in hands and feet, hot and cold flushes, and trembling and shaking. For a classification of panic disorder at least three attacks must have occurred within a three week period. Agoraphobia was regarded as one of the Phobic Disorders and classified separately, although the relevance of panic attacks to agoraphobic avoidance was recognised in the sub-categorisation of agoraphobia as either with or without panic attacks.

It was recognised after the introduction of DSM III that there were some difficulties and ambiguities with the system. Thus ongoing discussion led to the publication of the revised version, DSM III-R in 1987. The first striking difference in DSM III-R was the abolition of the separate categories of phobic disorders and anxiety states with all the anxiety disorders both phobic and non-phobic being classified under the heading of Anxiety Disorders. Clinical observations led to several important revisions in the classification of panic disorder. By this time it had become apparent that most cases of clinical agoraphobia developed secondary to panic attacks and rarely otherwise. These observations suggested that agoraphobia did not constitute a distinct syndrome in it's own right and was better seen as a consequence of the core disorder of panic attacks. Thus in DSM III-R agoraphobia was classified as secondary to panics in the classification of Panic Disorder With Agoraphobia, whereas those patients displaying no agoraphobic avoidance would be classified as Panic Disorder Without Agoraphobia. DSM III-R retained the category of Agoraphobia Without History of Panic Disorder but this was expected to be seldom used. The classification of panic attacks was also revised in DSM III-R to accommodate more recent observations. Firstly, the list of twelve symptoms was expanded to thirteen by the separation of fear of dying and fear of going crazy or doing something uncontrolled. These latter two symptoms were recognition of the

psychological element of panic attacks and the fact that the majority of patients expressed specific catastrophic fears as to the consequences of their panic attacks. A panic attack was again arbitrarily defined as comprising at least four of the thirteen symptoms and sudden onset was specified in DSM III-R as rising to a peak within 10 minutes of onset. DSM III-R also permitted a new classification for those panics which comprised less than the required four symptoms. These were defined as Limited Symptom Attacks and were suggested to be in all respects less severe than full-blown panic attacks of four symptoms or more. The actual classification of Panic Disorder was expanded in DSM III-R, again to accommodate a psychological perspective. A frequency criterion was retained in that four panic attacks occurring within a four week period would permit a classification of panic disorder. An additional or alternative criterion was added, however, in that a classification of panic disorder was also permitted if one or more panic attacks was followed by at least one month of persistent fear of subsequent attacks. Thus the psychological criterion of fear of panic attacks became an important part of the diagnosis which had previously, (in DSM III), been conceptualised in purely physical terms. Subsequent research and discussion has ratified this expansion to include psychological factors. The concept of persistent anxiety about bodily sensations related to panic has been variously termed, anxious apprehension (Barlow 1988), fear of fear (Goldstein & Chambless 1978) and anxiety sensitivity (Reiss & McNally 1985). Instruments designed to measure this construct (Chambless et al 1984, McNally & Lorenz 1987) have confirmed it as a hallmark of panic disorder to the extent that elevated anxiety sensitivity secondary to unexpected panic attacks is what distinguishes panic disorder from other anxiety disorders in which panic attacks occasionally occur (Taylor et al 1992). DSM III-R also introduced a rating of severity of panic attacks where "mild" was defined as, all attacks during the past month have been limited symptom attacks, or only one panic attack has occurred, "moderate" meant during the past month attacks have been intermediate between mild and severe, and "severe" meant that during the past month there have been at least eight panic attacks. These criteria of severity are essentially arbitrary and require empirical validation.

The criteria for agoraphobia in DSM III-R firmly defined this avoidance as secondary to panic attacks in that agoraphobia was classified as "fear of being in

places or situations from which escape might be difficult (or embarrassing) or in which help might not be available in the event of a panic attack" (DSM III-R 1987, p238). Severity of agoraphobia was also possible again on an essentially arbitrary scale ranging from "in remission" through "in partial remission" "mild", "moderate" to "severe". The main points of change in DSM III-R as compared to DSM III are that the classification of a panic attack was no longer based on solely physical symptoms with the inclusion of psychological symptoms in the list of thirteen symptoms. Agoraphobia was recognised as likely to occur secondary to panic disorder and was thus relegated to the status of a secondary qualification of a classification of panic disorder. Lastly, in recognition of the importance of psychological factors, particularly anxiety sensitivity or fear of fear in the development of panic disorder, the addition of the criterion of one month of continuous fear of recurrence following a single panic attack as an alternative to the frequency criterion of four panic attacks in the past four weeks was introduced.

As testament to the pace at which research proceeds in the area of panic, work on the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV 1994) began only one year after the publication of DSM III-R. The fourth revision was strongly influenced by Barlow (1988) who reported that panic attacks occurred across the full range of anxiety disorders. Thus in DSM IV panic attacks are defined separately from panic disorder and the classification of both has been clarified. The classification of a panic attack is the same as that in DSM III-R, namely four symptoms from the list of thirteen with a rise time within 10 minutes of onset. DSM IV further distinguishes between unexpected (uncued panic) attacks, situationally bound (cued) panic attacks, and situationally predisposed panic attacks. Unexpected panic attacks occur classically "out of the blue" and are not associated with any situational trigger. Although unexpected attacks are central to the diagnosis of panic disorder they do occur in other anxiety disorders (McNally 1994). Situationally bound attacks occur almost invariably and immediately on exposure to a situational trigger, and are characteristic of specific and social phobias. Situationally predisposed attacks have an increased probability of occurring on exposure to a trigger situation but do not invariably occur. They are typical in panic disorder with agoraphobia but can also occur in specific and social phobia (McNally 1994). The classification of panic disorder has also been revised and now requires both a

frequency criterion (repeated panic attacks), and the fear of recurrence of panic attacks criterion this being clarified as either, persistent concern about having further attacks, worry about the consequences of attacks, or a significant change in behaviour related to the attacks (DSM IV 1994). Thus in contrast to DSM III-R, under DSM IV a patient cannot qualify for a classification of panic disorder merely by experiencing a single panic attack followed by a persistent fear of subsequent attacks, or merely by experiencing repeated attacks without developing a fear of panic. Both aspects of the disorder are required under DSM IV. The classification of agoraphobia in DSM IV remains essentially unchanged from DSM III-R although the rating of severity has been dropped, as has that for panic disorder.

The studies to be presented in this thesis were all conducted before the introduction of DSM IV and thus used the definitions outlined in DSM III-R. The implications that any differences between the DSM III-R and DSM IV systems have for these studies will be discussed in Chapter 8.

1.4 Definition

The DSM III-R definition of panic disorder both with and without agoraphobia is given below.

1. Diagnostic Criteria for Panic Disorder

A. At some time during the disturbance, one or more panic attacks (discrete periods of intense fear or discomfort) have occurred that were (1) unexpected, i.e., did not always occur immediately before or on exposure to a situation that always caused anxiety, and (2) not triggered by situations in which the person was the focus of other's attention.

B. Either four attacks as defined in criterion A, have occurred within a four week period, or one or more attacks have been followed by a period of at least a month of persistent fear of having another attack.

C. At least four of the following symptoms developed during at least one of the attacks:

(1) shortness of breath (dyspnoea) or smothering sensations

(2) dizziness, unsteady feelings, or faintness

(3) palpitations or accelerated heart rate (tachycardia)

(4) trembling or shaking

(5) sweating

(6) choking

(7) nausea or abdominal distress

(8) depersonalisation or derealisation

(9) numbness or tingling sensations (parasthesias)

(10) flushes (hot flashes) or chills

(11) chest pain or discomfort

(12) fear of dying

(13) fear of going crazy or of doing something uncontrolled

Attacks involving four or more symptoms are panic attacks; attacks involving fewer than four symptoms are limited symptom attacks.

D. During at least some of the attacks, at least four of the C symptoms developed suddenly and increased in intensity within ten minutes of the beginning of the first C symptoms noticed in the attack.

E. It cannot be established that an organic factor initiated and maintained the disturbance, e.g., Amphetamine or Caffeine intoxication, hyperthyroidism.

2. Diagnostic Criteria for Panic Disorder With Agoraphobia

A. Meets the criteria for Panic Disorder as defined in section 1. above.

B. Agoraphobia: Fear of being in places or situations from which escape might be difficult (or embarrassing) or in which help might not be available in the event of a panic attack (includes cases in which persistent avoidance behaviour originated during an active phase of Panic Disorder, even if the person does not attribute the avoidance behaviour to fear of having a panic attack.) As a result of this fear, the

person either restricts travel or needs a companion when away from home, or else endures agoraphobic situations despite intense anxiety. Common agoraphobic situations include being outside the home alone, being in a crowd or standing in a line, being on a bridge, and travelling in a bus, train or car.

3. Diagnostic Criteria for Panic Disorder Without Agoraphobia

A. Meets the criteria for Panic Disorder as defined in section 1. above.

B. Absence of Agoraphobia as defined in 2. above.

1.5 Differential Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders was constructed to facilitate the separation of the anxiety disorders by listing criteria on which they can be differentiated. The underlying assumption is, of course, that such a differentiation is possible and is scientifically valid. Aronson (1987a) suggests that the anxiety disorders may not be as separable as the DSM system implies, and questions whether panic disorder can be viewed as a distinct diagnostic entity. Tyrer (1989) also argues that the anxiety disorders are most usefully classified under one diagnostic grouping, which he terms the "general neurotic syndrome". Thus whilst the DSM classification seeks that which is unique to each anxiety disorder, others such as Tyrer look to the commonalties that are shared amongst the disorders. Both positions find support in a recent factor analytic study (Zinbarg & Barlow 1996), which analysed data from self-report questionnaires completed by 423 patients with anxiety disorders and 32 non-patient controls. Questionnaires were chosen to cover a broad range of symptom presentation across differing DSM III-R anxiety disorders. Factor analysis revealed a higher order general factor common to all the anxiety disorders that differentiated the patient groups from the non-patient controls. Zinbarg & Barlow described this factor as "negative affectivity", arguing that a dispositional tendency towards experiencing negative affective states underlay all of the DSM III-R anxiety disorders. Several lower order factors provided the basis for differentiating amongst the individual anxiety disorders, as did a number of factors derived from a discriminant function analysis. This most recent work suggests that there are both commonalities and

unique properties for each anxiety disorder. Attention must still be paid to the boundaries of the classification of panic disorder. There has been considerable debate as to whether panic disorder is a separate diagnostic entity or whether it is better regarded simply as a more intense form of generalised anxiety. This debate often confounds two different questions. Firstly, can a panic attack be differentiated from anxiety, or is it simply a more intense form of the same emotion, and secondly, can panic disorder be differentiated from generalised anxiety disorder or is the level of diagnostic overlap such that they are best regarded as different facets of the same disorder? For panic disorder to be a separate diagnostic entity it is important to show not only that the central symptom complex, the panic attack, can be differentiated from other forms of anxiety, but also that the syndrome itself can be distinguished from other anxiety disorders.

In discussing the clarity of panic disorder as a diagnosis, Tyrer confidently asserts that "....there is no doubting the clarity and reliability of its main feature, the panic attack" (Tyrer 1989 p25). For this certainty to be justified the defining features of a panic attack should be readily observable. A panic attack should therefor be distinguishable from anxiety by being, of sudden onset, involving notable physiological arousal and being characterised by feelings of fear and impending catastrophe. Several lines of evidence justify this distinction. Regarding abruptness of onset, Argyle & Roth (1989a, 1989b) found, in a study of 90 patients with panic disorder, that episodes of severe anxiety with gradual onset were not associated with fears of dying or going crazy, nor were they associated with as many symptoms as were episodes of anxiety with a rapid onset, i.e. panic attacks. Evidence for increased physiological arousal in panic attacks as compared to anxiety is found in prospective studies employing physiological measurement. Taylor et al (1986) had panic patients record both anticipatory anxiety and panic over a 6 day period. They found that in periods of intense anticipatory anxiety heart rate remained relatively stable, and importantly was significantly lower than heart rate recorded during panic attacks. Heart rate averaged 89.2 BPM during anticipatory anxiety and 108.2 BPM during panic attacks, despite patients' subjective ratings of intensity of the two types of anxiety being virtually identical. In a similar design Freedman et al (1985) measured heart rate during self-reported panic attacks and also during "control periods" where anxiety was rated as equally intense but was not labelled as panic. Abrupt heart rate

increases occurred during the panic episodes but not during the control periods, again indicating the suddenness of onset and characteristic physiological arousal attributed to panic attacks. This abruptness of onset is not consistent with the notion that panic is continuous with lower levels of anxiety and simply a more intense form of them. Were this the case, panic attacks would be expected to occur following a period of build up of, or at least the presence of, underlying anxiety. The finding that panic attacks can occur during periods of relaxation and even during sleep (i.e. relaxation induced panic, Adler et al 1987), indicates that panic attacks can occur discontinuous with anxiety state (Uhde & Mellman 1987). Investigations of patterns of appraisal and cognitive content also reveal differences between anxiety and panic. Both Hibbert (1984) and Rapee (1985) observed more intense cognitions focusing on physiological, psychological or social disaster in panic patients than in patients without panic. Rapee et al (1992) studied 90 patients with panic disorder (DSM III-R) who also had an additional diagnosis of either simple or social phobia and compared cognitive content during panic attacks with that during anxiety experienced during exposure to feared objects or situations. They found that fears of dying and fears of going crazy/loosing control were more frequently experienced during panic attacks than during phobic anxiety. This pattern of catastrophic cognition in panic patients finds further elaboration in the Cognitive Model of panic (Clark 1986, 1988, Beck & Emery 1985, Beck 1988). Some caution is warranted in interpreting these findings. As Barlow (1988) points out, such differences in cognitive style may be epiphenominal, reflecting defining characteristics of patients falling into the category of panic disorder rather than something fundamental about panic itself.

The evidence above indicates, at least tentatively, that panic is separable from anxiety. What of the distinction of the clinical syndromes, is panic disorder distinct from generalised anxiety disorder? Again several lines of evidence would suggest this to be the case. As previously mentioned the contemporary distinction between panic disorder and generalised anxiety disorder is based on the differentiation of symptom presentation (Roth 1960) and also on the distinction in response to pharmacological treatment, or pharmacological dissection, proposed by Klein (e.g. Klein 1981). Several more recent discussions (Barlow 1988, McNally 1994) have questioned the theoretical and clinical validity of the concept of pharmacological dissection. The

notion of difference in symptom presentation is however supported in studies that compared panic disorder with generalised anxiety disorder patients on a range of symptom measures. Several studies indicated that panic disorder patients reported a greater somatic component in symptoms than generalised anxiety disorder patients did (Hoehn-Saric 1982, Barlow et al 1984, Anderson et al 1984, Rapee 1985). This difference was restricted to somatic symptoms, however, with reports of psychic or cognitive symptoms of anxiety being similar across both patient groups (Barlow et al 1984, Anderson et al 1984, Rapee 1985, Noyes et al 1992). This finding is interesting in that panic disorder patients evidently do not score higher than generalised anxiety disorder patients on scales of general anxiety as might be the case if panic disorder were simply a more intense form of generalised anxiety disorder. Panic disorder patients do score higher than generalised anxiety disorder patients on measures of anxiety sensitivity such as the Anxiety Sensitivity Index (ASI, Reiss et al 1986). Thus although both disorders experience anxiety symptoms, only the panic disorder patients show a marked fear of and sensitivity to these symptoms leading McNally (1992) to suggest that this validates the distinction between panic disorder and generalised anxiety disorder. Other research has indicated that panic disorder patients report a greater incidence of negative affect such as depression and irritability (Hoehn-Saric 1982) and a greater incidence of major depressive episodes prior to the onset of their anxiety disorder (Raskin et al 1982), than do generalised anxiety disorder patients. Genetic and family aggregation studies also indicate differences that are consistent with the separation of the disorders. Panic disorder and panic attacks have been shown to aggregate in families (Crowe et al 1983, Crowe 1990) whereas such aggregation has not been consistently found for generalised anxiety disorder (Noyes et al 1992). Of the twin studies which have been published the first, Torgersen(1983) found that monozygotic (MZ) twins had a rate of DSM III panic disorder and agoraphobia with panic attacks five times that for dizygotic (DZ) twins. In the same study, there was no significant MZ vs. DZ difference found for generalised anxiety disorder. These results have been taken as indicative of a specific genetic linkage for PD but not for GAD (Weissman 1990). Results from more recent twin studies suggest the difference is less clear cut. Further twin studies have indicated increased MZ vs. DZ rates of DSM III-R panic disorder of similar magnitude to the original Torgersen study (Kendler et al 1993, Skre et al

1993). For generalised anxiety disorder, a recent Australian study using DSM III criteria found an increased MZ vs. DZ concordance rate (Andrews et al 1990). Although this difference failed to reach statistical significance it was taken as an indication of a possible genetic component to generalised anxiety disorder. In a more detailed analysis of DSM III-R generalised anxiety disorder in women Kendler et al (1992) also found an increased MZ vs. DZ concordance rate which was greatly reduced when generalised anxiety disorder cases with concomitant depression were excluded. This led others (Skre et al 1993) to argue that concomitant mood disorders are a major influence on twin concordance rates for generalised anxiety disorder. Genetic and family aggregation data would seem to suggest that there is reasonably strong evidence for genetic linkage in panic disorder whereas the case is more equivocal for generalised anxiety disorder. The limitations of these twin studies must also be borne in mind when considering their results. Samples were small and subjects were rarely assessed blindly for zygosity, diagnosis, or probands' diagnosis. Overall there is sufficient evidence to suggest that the separation of panic disorder from generalised anxiety disorder has some basis and this supports the distinction made in the DSM classification systems.

1.6 Prevalence

Whilst definition of disorder and method of survey will inevitably affect prevalence, panic disorder whether with or without agoraphobia, is regarded as a clinically prevalent condition. Psychiatric disorders have only relatively recently become the subject of epidemiological enquiry with the absence of explicit diagnostic criteria and the lack of any reliable means of establishing caseness restricting investigations. The establishment of diagnostic criteria in DSM III and the incorporation of such criteria into protocols such as the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS, Robbins et al 1981) made epidemiological enquiry possible. The largest and most ambitious investigation of the prevalence of mental disorders undertaken to date is the Epidemiological Catchment Area survey (ECA). The DIS was developed for the ECA study and was administered by lay interviewers to a probability sample of n=18,000 adults drawn from five communities in the United States. The ECA study indicated lifetime prevalence rates for DSM III panic disorder of 2.1% for women and 1.0% for men giving a combined lifetime prevalence

of 1.7%. Panic disorder was most common amongst subjects aged 30-44 years, and least common among subjects who were over 65 years. Subjects with panic disorder were found to seek the help of mental health professionals more than subjects with any other mental health disorder (Weissman 1985, Robins & Regier 1991). These relatively low prevalence estimates for panic disorder lead Eaton et al (1991) to conclude that "Panic disorder is not very prevalent in the population " (Eaton et al 1991, p159). The ECA diagnoses were made using DSM III under which panic disorder and agoraphobia with panic attacks were classified as separate disorders. Agoraphobia shows much higher prevalence rates in the ECA survey with lifetime rates of 7.7% for women and 2.9% for men (Robins & Regier 1991). There is considerable dispute however over the reliability and accuracy of the ECA classifications of agoraphobia both with and without panic attacks (McNally 1994). Indeed in a reanalysis of some of the ECA samples Howarth et al (1993) found examples of misclassifications among the phobic disorders leading to grossly inflated estimates for agoraphobia without panic attacks and possibly low estimates for agoraphobia with panic attacks. Others have also disagreed with Eaton et al's (1991) characterisation of panic disorder as an uncommon condition. Katon et al (1987) suggested that the DIS had high specificity but low sensitivity and thus failed to pick up many cases of panic disorder due to the way the panic disorder target question was phrased. Subjects were asked "have you ever had a spell or attack when all of a sudden you felt frightened, anxious or very uneasy in situations when most people would not be afraid?" (Robins & Regier 1991, p408). Katon et al (1987) observed that since panic disorder patients fear the symptoms of the panic attacks themselves and not the situations in which they occur, many panic patients might respond to this question in the negative on the grounds that anyone who felt like they did in such situations would feel frightened too. Thus the DIS may underestimate the prevalence of panic disorder. Subsequent studies using DSM criteria but different interview schedules to establish caseness have found higher prevalence rates for panic disorder. In a study employing DSM III criteria and a DIS modified in the light of the above discussion Katon (1986) quote a lifetime prevalence rate of 6.7% in a sample of n= 195 adults screened in a primary care practice. In a study employing DSM III-R criteria established via the Structured Clinical Interview for DSM III-R (SCID, Spitzer et al 1988) Katerndahl & Realini (1993) evaluated a sample of 1,306

residents of San Antonio Texas, finding lifetime prevalence estimates of panic disorder of 4.1% for women and 1.5% for men with a combined rate of 3.8%. Katerndahl & Realini (1993) explained their lifetime prevalence rate of nearly double the ECA figure as arising due to the more sensitive SCID detecting more genuine cases of panic disorder than the relatively insensitive DIS. The DIS is also reportedly notably less reliable than other interview schedules (McNally 1994). Reliability studies using the DIS have yielded kappa values of between .40 (Robbins et al 1981) to -.20 (Anthoney et al 1985) for panic disorder. These reliability estimates compare very unfavourably with studies using either the Anxiety Disorders Interview Schedule (ADIS-R, DiNardo & Barlow 1988) and DSM III-R criteria which yielded a kappa of .75 for panic disorder with or without agoraphobia (DiNardo et al 1993), or those using the Structural Clinical Interview for DSM III-R (SCID, Williams et al 1992a) which yielded kappas of .87 and .73 for panic disorder with and without agoraphobia respectively (Williams et al 1992b). The data does suggest, however, that panic disorder both with and without agoraphobia can be reliably diagnosed.

1.7 Antecedents and Consequences

Having discussed the classification, syndromal validity and estimated prevalence of panic disorder with and without agoraphobia, attention now turns to broader issues related to it's clinical presentation including the possible consequences of the disorder for sufferers. Panic disorder might be described as a disorder of early adulthood. In the ECA study, panic disorder had a mean age of onset of 24 years (Burke et al 1990). Agoraphobia has also been reported to have a similar mean age of onset in earlier studies (Burns & Thorpe 1977, Marks & Herst 1970). The lifetime prevalence for panic disorder in the ECA study was twice as high for women as for men (Eaton et al 1991), as was that in the Katerndahl & Realini (1993) study. Reviewing recent studies Clum & Knowles (1991) found that women constituted 59% of cases of DSM III-R panic disorder without agoraphobia and 89% of cases of panic disorder with agoraphobia. Comparisons of male and female panic disorder patients have, however, revealed no differences in phobic severity, assertiveness, neuroticism, extraversion (Mavissakalian 1985), panic frequency (Chambless & Mason 1986), panic severity, trait anxiety, age of onset, and duration of illness (Oei et al 1990). Chambless & Mason (1986) did find that both male and female

agoraphobics scored below population norms for their respective gender on scales of masculine gender-role behaviour, leading to the speculation that cultural or other factors which discourage masculine methods of coping with panic may predispose towards the development of agoraphobic avoidance. Many factors have been suggested as possible precipitants for the onset of panic disorder particularly negative life events. Barlow notes that "a remarkably consistent observation of biological and psychological clinicians and investigators has been the evidence of negative life events preceding the first panic attack in patients who later present with panic disorder and agoraphobia." (Barlow 1988, p215). This suggestion of panic disorder arising during stress resulting from negative life events has great face validity for the practising clinician and is consistent with the findings of generalised anxiety preceding the emergence of panic (Fava et al 1988, 1992, Garvey et al 1988) and uncontrolled investigations of life events in panic disorder patients (Lteif & Mavissakalian 1995). Controlled studies also support the position. In an early study, Roth (1959) found that a sample of n= 135 agoraphobics reported significantly more stressful events prior to the onset of their agoraphobia than did a control group of patients with "other neurotic disorders". Similarly Faravelli & Pallanti (1989) reported that panic patients experienced more serious negative life events in the year prior to the onset of their panic disorder than did a group of age-sex matched healthy controls. Other studies suggest it is not the increased occurrence of negative life events per se which is important, but the way in which such events are perceived. In two studies (Roy-Byrne et al 1986, Rapee et al 1990) panic patients reported no more life events during an equivalent time frame than did control groups of other anxiety disorders and healthy subjects. The panic patients in both studies rated the life events as more distressing, uncontrollable and undesirable and having a more negative impact on their lives than did subjects in the control groups. Thus the perceived negative impact of life events may be at least as important as their frequency. Accurately assessing the aetiological significance of life events is difficult. The fact that such events occur prior to the onset of panic disorder and are often perceived by patients as being salient does not establish a causal role for them. Stressful life events would nonetheless seem to have a potential role in the precipitation of panic disorder. Researchers have also uncovered a host of other factors that may influence the occurrence of panic disorder or exacerbate an existing

disorder. The list of possible factors ranges from withdrawal from alcohol (Kushner et al 1990) or nicotine (Brodsky 1985), use of both illegal drugs and over-the-counter proprietary cold medications containing pseudoepinephrine (Roy-Byrne & Uhde 1988), to anxiety provoking visual stimuli such as fluorescent strip-lighting (Watts & Wilkins 1989). In contradiction to early studies, recent research has confirmed a pattern of pre-menstrual exacerbation of panic symptoms with a prospective self-report study of 24 female panickers finding a 100% increase in panic attack frequency premenstrually (Kaspi et al 1994). The research discussed so far implicates a wide variety of factors in the precipitation of panic disorder. It is perhaps surprising then that the first panic attack occurs so often in situations typical of the panic-agoraphobic symptom complex, that is in crowded public places or in restricted or enclosed situations often distant from the patients home (Barlow 1988, Lelliot et al 1989, Faravelli et al 1992). Some have attempted to explain the preponderance of "agoraphobic" situations among first panic attacks. Principal amongst these is Nesse (Nesse 1984, 1987,1988) who argues for an evolutionary perspective in which agoraphobic situations can be viewed as prepared fears. In early hominid societies situations which involved being in enclosed spaces or exposed in open ground, being far from home territory or amongst strangers or any of these in the absence of a trusted companion would represent a significant threat to well-being. Thus it would be advantageous to respond readily with anxiety to such situations. Nesse (1987) further suggests a threshold model for the triggering of panic attacks suggesting that this threshold is lowered in vulnerable individuals under pressure, who then respond with a panic attack when in an agoraphobic triggering situation. If this first panic attack is responded to with fear the cycle of anxiety sensitivity is set in train and the panic disorder characterised by repeated panic attacks develops (Barlow 1988). This interesting speculation receives some support from a study which suggest that panic attacks do operate as initiating traumatic stressors (McNally & Lukach 1992), and from a study which found that 71% of a sample of 57 patients with panic disorder with agoraphobia reported fleeing immediately on experiencing their first panic attack (Lelliot et al 1989). Nesse's evolutionary model has also been adopted as a useful explanatory construct in psychological treatment packages (Shear et al 1994).

Explanations for precipitation and onset aside there is little doubt that once established panic disorder is a distressing and disruptive condition that leads to sufferers making heavy demands on treatment services and resources. Regarding service usage, Uhlenhuth et al (1983) in a symptom checklist survey conducted on a general population and relating symptom grouping to psychotherapeutic drug use, found that the group defined as the "panic-agoraphobia complex" used more and a wider range of psychotropic medications than any other diagnosis. Using samples from the ECA study data (Robbins & Reiger 1991), others (Boyd 1986, Klerman et al 1991) have also shown that panic disorder patients are heavy users of ambulatory mental health and general healthcare facilities. In the only such study conducted on a UK sample Simpson et al (1994) compared a sample of 100 DSM III-R panic disorder with and without agoraphobia patients with 100 age sex matched controls from the same general practice lists on a range of indices of service usage, reported symptoms and diagnosed major and minor illnesses. This study found that panic patients had significantly higher surgery attendance rates, secondary referrals, clinical tests and investigations, and prescriptions for psychotropic and non-psychotropic medications than did the controls. There were no differences between the patients and controls in rates of major illnesses but significant difference in minor illnesses particularly respiratory, genitor-urinary and cardio-vascular minor illnesses. The clinical perception of panic disorder patients as frequent clinic or surgery attenders who receive repeated clinical investigations and frequent medication is supported by the findings of these studies. Panic disorder also impacts on individuals health and treatment service usage in other ways being associated with increased risk for other anxiety disorders and for depression (Wittchen & Essau 1993), for alcohol abuse (George et al 1990) and increased risk of suicide attempt (Johnson et al 1990, Noyes et al 1991a, Lepine et al 1993) although in the latter case debate continues as to the significance of co-morbid diagnoses to this increased risk (Hornig & McNally 1995). The relevance of panic disorder to general health is also suggested by two studies which have found reduced immune system function (Ramesh et al 1991) and increased allergenic sensitivity and allergic response (Schmidt-Traub & Bamler 1997) in panic disorder patients as compared to controls. If even only a proportion of these suggested risks consequent on a diagnosis of panic disorder are accurate, given the prevalence rates suggested for panic disorder earlier, it represents a significant drain

on healthcare resources. This is especially so given that in the absence of treatment panic disorder is argued to have a chronic or at best fluctuating course with few cases of genuine full remission (Wittchen & Essau 1993, Otto & Whittal 1995). Furthermore panic disorder has been found to present predominantly in the primary care setting (Ashcroft et al 1987, Katerndahl & Realini 1995) where resources available to tackle the disorder are limited. It is in this context that treatments for the disorder must be considered.

1.8 Treatment

The clinical prevalence, distressing nature and clinical consequences of a classification of panic disorder lend considerable impetus to the search for adequate treatments for the disorder. It is not surprising therefor that the past three decades have seen a proliferation in the number of treatment outcome studies published on panic disorder. This comparatively large literature demarcates along professional lines, with pharmacological treatments advocated by psychiatry/pharmacology and psychological treatments championed by psychologists. This has led some to characterise the resulting discussion as "..a partisan debate among various interest groups who have become zealous in their advocacy of their preferred treatment models" (Jacobson & Hollon 1996 p74). It is the intention in this section to briefly review the findings of the treatment outcome literature for both pharmacological and psychological treatments for panic disorder.

1.8.1 Pharmacological Treatments

Drug treatments have influenced the nosology of panic disorder and are arguably the most commonly used treatment for the disorder. A wide variety of drugs have been advocated and investigated as potential treatments for panic. The following discussion will focus on the most common of these.

1.8.1.1 The Tricyclic Antidepressants

The most commonly studied drug in the treatment of panic disorder is the tricyclic antidepressant imipramine. This was the drug used in the groundbreaking early work of Klein (Klein & Fink 1962, Klein 1964). In subsequent placebo controlled studies (Zitrin et al 1980, 1983), imipramine proved superior to placebo on global measures

of improvement and on retrospective ratings of panic attacks. Importantly, in these early controlled studies, imipramine was usually given in combination with psychological treatments, either exposure in vivo or supportive psychotherapy. The finding of superiority of imipramine over placebo when given in combination with psychological treatments was replicated in the work of Mavissakalian and colleagues (Mavissakalian et al 1983, Mavissakalian & Michelson 1986). Others have failed to replicate this finding. In a four-way double-placebo comparison of imipramine plus exposure, imipramine plus relaxation training, placebo plus exposure, and placebo plus relaxation training, Marks et al (1983) found no difference between imipramine and placebo. A subsequent reanalysis of this data (Raskin 1990) did however suggest that imipramine was superior to placebo on ratings of anticipatory anxiety and retrospective ratings of panic attacks. A later study which incorporated the prospective monitoring of panic attacks in a three group comparison of imipramine plus exposure, placebo plus exposure and imipramine plus anti-exposure (Telch et al 1985), found no significant between-group differences in frequency of panic attacks at end-point (8 week) analysis. Within-group comparisons revealed a significant reduction in panic attacks for the imipramine plus exposure group only. As a result of these findings some (McNally 1994) have suggested that imipramine may reduce panic attacks only in the presence of exposure treatments. This is reinforced by a placebo controlled study where imipramine was given in the absence of psychological treatments. Evans et al (1986) compared imipramine, placebo and the novel serotonin re-uptake inhibitor zimelidine. Rating scales for general anxiety, agoraphobic avoidance and depression suggested the superiority of zimelidine over both imipramine and placebo, there being no statistically significant differences between imipramine and placebo. This study was an early indication of the relevance of serotonin specific drugs to the treatment of panic disorder. Zimelidine was, unfortunately, taken off the market due to an apparent increased risk for Guillian-Barre Syndrome. In summary, most studies have shown that imipramine benefits panic disorder and agoraphobia at least when given in combination with exposure treatments. There are several suggested hypotheses for the effectiveness of imipramine. The original hypothesis, the basis of Klein's pharmacological dissection, is that imipramine blocks panic attacks and affects secondary avoidance only through this mechanism. Some studies support this assertion (Klein et al 1987) while others

(Telch et al 1985) do not. Others (Marks et al 1983) have suggested that imipramine exerts it's effect through it s antidepressant action with any benefits to panic and agoraphobia being secondary to this. Research evidence does not support this case with patients showing benefit with imipramine even when they exhibit few symptoms of depression (Clum & Pendrey 1987). A further hypothesis is that imipramine exerts an effect through the reduction of anticipatory anxiety characteristic of panic disorder patients (Barlow 1988). In support of this hypothesis Kahn et al (1986), found that imipramine benefited patients with GAD, suggesting that the drug attenuated the somatic symptoms underlying both panic attacks and anticipatory anxiety. As McNally (1994) points out, this is in keeping with the effect of imipramine on the supposed noradrenergic dysfunction underlying both forms of anxiety. This is in direct contradiction to the original view of imipramine as the panic specific drug implicated in Klein's pharmacological dissection.

Other tricyclic drugs have also shown efficacy when used in the treatment of panic disorder. Clomipramine, a tricyclic antidepressant that blocks the reuptake of serotonin as well as noradrenaline, has shown superior efficacy when compared to placebo (Johnson et al 1988, Modigh et al 1992) and imipramine (Modigh et al 1992). These findings led Modigh et al (1992) to suggest that serotonergic drugs may have a more potent anti-panic action than noradrenergic drugs. Others (Fahy et al 1992) have found that the superiority of clomipramine over placebo is reduced when both are combined with behaviour therapy.

1.8.1.2 Monoamine Oxidase Inhibitors

The second class of antidepressant drugs investigated for panic disorder is the monoamine oxidase inhibitors (MAOI). These drugs inhibit the action of the enzyme monoamine oxidase which deactivates monoamines such as serotonin, noradrenaline, dopamine and tyramine, thus increasing the availability of these monoamines in the central nervous system. The little research available on these drugs is equivocal with one study employing the MAOI phenelzine (Tyrer et al 1973) finding no advantage over placebo, whilst a later study (Sheehan et al 1980), found an advantage over placebo and imipramine for phenelzine. It is impossible to judge the anti-panic efficacy of phenelzine as neither of these studies incorporated any measures of panic attacks. This lack of controlled evidence combined with the danger of potentially

fatal hypertensive crises if certain foodstuffs are ingested have limited the usefulness and use of the MAOIs in the treatment of panic disorder.

1.8.1.3 Benzodiazepines

Benzodiazepines have been shown to have efficacy in the treatment of panic disorder. The most widely studied benzodiazepine is the high potency triazolobenzodiazepine, alprazolam. The efficacy of alprazolam was investigated in the largest pharmacological treatment outcome study in panic disorder conducted to date. The Cross-National Collaborative Panic Study (Klerman 1988) was a multi-centre study conducted in two phases. The first phase established the superiority of alprazolam over placebo on measures of spontaneous and situational panic, anticipatory anxiety, and phobic avoidance. In this study 59% and 32% of the alprazolam and placebo groups were panic free at treatment end-point (Ballenger et al 1988). Phase two of the study involved a multi-centre three-way comparison of alprazolam, imipramine and placebo which again revealed a superiority of active drug over placebo but few significant differences between the active drugs alprazolam and imipramine (Cross National Collaborative Panic Study 1992). Others (Marks et al 1989) have questioned the validity of the drug-placebo difference found for alprazolam suggesting that this difference existed early in treatment only and that if the trial were continued long enough the drug-placebo difference would disappear as the placebo group began to improve. Marks et al (1993) also failed two replicate the alprazolam placebo difference in a four group double-placebo design employing alprazolam plus exposure, alprazolam plus relaxation training, placebo plus exposure, and placebo plus relaxation training. Further difficulties with alprazolam arise when the drug is discontinued. In the Cross National Collaborative Panic Study fully 82% of patients given alprazolam relapsed on withdrawal of the drug (Pecknold et al 1988). In a similar withdrawal study Rickels et al (1993) found that 63% of their sample suffered a marked withdrawal syndrome lasting around three weeks, whilst 52% of their alprazolam patients suffered a rebound in panic frequency which exceeded baseline levels. Similar discontinuation problems were reported by Noyes et al (1991b), while Otto et al (1993) found that the addition of cognitive behavioural therapy facilitated the discontinuation of alprazolam. Thus despite it's initial promise, the discontinuation problems with alprazolam limit its clinical usefulness.

Other lower potency benzodiazepines have also shown efficacy for panic disorder if used in high doses. Three placebo controlled trials (Hafner & Marks 1976, Noyes et al 1984, Dunner et al 1986) have shown a statistical superiority over placebo for diazepam, whilst a similar result was obtained for the newer high potency benzodiazepine clonazepam (Tesar et al 1991). This evidence of efficacy is not matched by investigations of discontinuation effects however, and, given the findings for alprazolam caution would be advised.

1.8.1.4 Beta-Adrenergic Blockers

Beta-blockers counteract the peripheral effects of the sympathetic nervous system and thus reduce symptoms such as sweating, trembling and tachycardia. Thus these drugs have considerable intuitive appeal as a treatment for panic disorder. This appeal is not matched by research findings. There is limited controlled research on the drug but that which exists is not supportive. Noyes et al (1984) found propranolol ineffective against panic, a result supported by a later study (Munjack et al 1989) comparing propranolol, alprazolam and placebo. Despite one early study (Kathol et al 1980) which did find drug-placebo differences the consensus is that "the outlook for the use of beta-blockers in the treatment of panic is bleak" (Barlow 1988 p442).

1.8.1.5 Selective Serotonin Reuptake Inhibitors

In support of the suggestion (Modigh et al 1992) made earlier (section 1.8.1.1.) regarding drugs affecting the serotonin systems, recent evidence has suggested considerable efficacy for relatively new group of drugs. These antidepressant drugs, known as the selective serotonin reuptake inhibitors (SSRI), selectively block the reuptake of serotonin at the synapse thus increasing the availability of this neurotransmitter. In an uncontrolled open label study Gorman et al (1987) found the drug fluoxetine to be an effective anti-panic agent with 7 out of 16 patients studied becoming panic free at treatment end-point. Oehrberg et al (1995) also found the SSRI paroxetine superior to placebo on a range of panic related measures. Both paroxetine and placebo were given with cognitive behaviour therapy in this study. Most research on the SSRIs has been conducted using the drug fluvoxamine. Studies have shown fluvoxamine to be superior to placebo (Den Boer et al 1987, Den Boer

& Westenberg 1988, 1990, Hoehn-Saric et al 1993, Black et al 1993a, De Beurs et al 1995), the specific noradrenaline reuptake inhibitor maprotalin (Den Boer & Westenberg 1988), the serotonin antagonist ritanserin (Den Boer & Westenberg 1990), and brief cognitive therapy (Black et al 1993a). Fluvoxamine was also found to be of equivalent potency to clomipramine (Den Boer et al 1987). In a controlled comparison of fluvoxamine plus exposure, placebo plus exposure, panic management plus exposure, and exposure alone, De Beurs et al (1995) found the combination treatment of fluvoxamine plus exposure to be more effective than the other three treatment groups. These findings for fluvoxamine have led some to suggest that "...fluvoxamine warrants further investigation as an especially promising antipanic agent" (McNally 1994 p103). This enthusiasm may be further encouraged by the single study to date investigating discontinuation effects with fluvoxamine. Black et al (1993b) studied the patients treated in their outcome study (Black et al 1993a) following a further 8 months of additional treatment. They identified a mild withdrawal syndrome characterised by dizziness, nausea, headaches and irritability. Only one patient in their sample experienced a return of panic. These initial results suggest an impressive lack of withdrawal and rebound effects associated with the discontinuation of fluvoxamine, but require replication before firm conclusions can be drawn.

1.8.1.6 Other Drugs

The search for effective antipanic agents has also included studies on other drugs less obviously related to panic disorder, usually with limited or negative findings. Thus the non-benzodiazepine anti-convulsants carbamazepine (Uhde et al 1988) and valproate (Keck et al 1993) were found to be of limited value in the treatment of panic disorder. A similar result was obtained in a study of the non-benzodiazepine anxiolytic buspirone (Robinson et al 1989).

1.8.2 Psychological Treatments

Psychological treatments have a 30 year history as treatments for anxiety disorders (McNally 1994). Psychological treatments targeted at panic attacks are more recent. The concept of panic attacks arose within the biological tradition, as did the notion

of specific panic focused treatment by drugs. Most early studies of behavioural treatments did not distinguish panic from other forms of anxiety either conceptually or operationally in clinical assessment. Most of these studies investigated behavioural treatments or agoraphobia, presumably in many cases with associated panic attacks. The effect of these treatments specifically on panic attacks is unknown as panic was not operationalised or measured.

1.8.2.1 Early Treatments

Early treatment techniques were based on laboratory findings from conditioned fear experiments usually conducted on animal analogues. Wolpe (1958) found that cats lost their conditioned fear of specific stimuli if they were fed in settings increasingly similar to the initial conditioning situation. Wolpe interpreted this finding as indicating that the stronger feeding response had inhibited the fear response and termed this action "reciprocal inhibition" (Wolpe 1958). Employing the principle of reciprocal inhibition in the treatment of fears that were presumed to be acquired via conditioning Wolpe developed the treatment technique systematic desensitisation. This involved the repeated pairing of the fear stimulus with fear inhibiting responses, usually progressive muscle relaxation. A hierarchy of stimulus situations was first confronted in imagination with the later transfer of practice to real life situations. Early treatment outcome studies with agoraphobic patients produced equivocal results with improvements after 16-20 sessions being limited at best (Gelder & Marks 1966, Gelder et al 1967). These limited gains following considerable clinical input prompted a search for faster and more effective treatments. Stampfl & Levis (1967) developed their "implosion therapy" as a theoretical and clinical alternative. Based on Mowrer's (1939) two-factor conditioning theory of fear and avoidance where classically acquired fears were maintained and reinforced by avoidance operants, Stampfl & Levis (1967) argued that neurotic symptoms could be eliminated by the extinction of the conditioned fear that motivated the avoidance, this being best achieved by maximal exposure to the feared stimulus. Thus the treatment technique of flooding developed. This was principally conducted in imagination and required the patient to maximise their fear by imagining extremely frightening scenes until their discomfort and anxiety diminished. Claims for the effectiveness of imaginal flooding led to its use with agoraphobics. In a cross-over design employing imaginal

flooding or imaginal desensitisation with agoraphobic and specific phobic patients, Marks et al (1971) found that, although overall treatment effects were not large, flooding was more effective than desensitisation for the agoraphobics, leading the authors to conclude that the relaxation and graduated exposure central to the systematic desensitisation treatment are unnecessary in the treatment of agoraphobia. A subsequent study (Stern & Marks 1973) suggested that real-life or in vivo, exposure was more effective than imaginal, and that massed rather than sporadic practice was most effective. These basic principals of massed practice of in vivo exposure, remain the foundation of behavioural treatments for agoraphobia to date. This exposure was conducted with the therapist present throughout.

1.8.2.2 Exposure Based Treatments

Despite some early contradictory findings of equivalence between imaginal and in vivo exposure from the Oxford research group (Gelder et al 1973, Mathews et al 1976), the vast bulk of experimental evidence indicates a degree of efficacy for treatments for agoraphobia based on the principal of repeated prolonged exposure to the feared stimulus situations (Jansson & Ost 1982, Jacobson et al 1988). This efficacy is maintained in long term follow up studies conducted over 4-7 years post treatment (Emmelkamp & Kuipers 1979, McPherson et al 1980, Munby & Johnson 1980). In vivo exposure continues to date to form the basis of much of the psychological treatment offered for agoraphobia (and by this fact, panic attacks) (Marks 1987). There has been some debate over the finer details of the conduct of the exposure, with some suggesting that practice can be either massed or spaced by individual preference (Chambless 1990), whilst others argue that the diminution of anxiety during exposure sessions is not a hard and fast requirement of adequate treatment (Rachman et al 1986). Nonetheless the basic treatment principal of exposure to real life feared object or situation endures. The requirement that exposure be conducted with the therapist present during sessions led Marks (1987) to suggest that exposure is "boring, time-consuming and expensive" (Marks 1987 p466). More recent work indicated that the presence of the therapist during sessions i.e. therapist accompanied exposure was indeed a cumbersome and unnecessary procedure, and that patients could construct and conduct their own exposure programmes. This idea forms the basis of the programmed practice self-exposure

treatments developed by Mathews and colleagues (Mathews et al 1981). This represented a significant advance in treatment delivery where patients conducted their own exposure sessions with possible support from spouse or partner, thus little therapist time was required. Exposure treatments have limitations however mainly in that gains can be limited and drop out rates high (Clum 1989), this leading Jacobson et al (1988) in their review to conclude that "exposure alone does not seem to be a total solution to the problem of agoraphobia" (Jacobson et al 1988 p552).

1.8.2.3 Treatments Adjunctive to Exposure

The acceptance of the limitations of exposure based treatments led on to a search for adjunctive treatment techniques that might enhance efficacy. Some groups suggested that spouse involvement in exposure treatments may be useful, although findings are equivocal with some supportive (Barlow et al 1984) whilst others found no advantage to spouse involvement (Cobb et al 1984). Other research stemmed from a conceptualisation of agoraphobia as a tripartite syndrome encompassing disturbances in behavioural, cognitive, and physiological systems. As traditional exposure treatments had emphasised the behavioural expression of the disorder, additional treatments that targeted the other systems were investigated. In a series of three studies Emmelkamp and colleagues investigated the effects of adding cognitive procedures to exposure in vivo (Emmelkamp et al 1978, 1986, Emmelkamp & Mersch 1982). In these studies Rational-emotive therapy RET (Ellis 1962) and self-instructional training SIT (Meichenbaum 1977) were used. These treatments (RET, SIT), attempt to identify and replace maladaptive inner monologues with coping self-statements and to identify and change the irrational assumptions presumed to underlie the phobic behaviour. In these early studies the addition of these particular cognitive techniques did not significantly enhance the effects of exposure in vivo. Williams & Rapopport (1983) also compared exposure in vivo with exposure in vivo plus SIT for a group of agoraphobics with specific fears of driving. Again they found that for this rather restricted group, both groups improved significantly on self-rated anxiety with there being no advantage gained with the addition of SIT to exposure in vivo. Two later studies (Marchione et al 1987, Michelson et al 1988) compared the relative and combined efficacies of therapist assisted graduated exposure, relaxation training, and cognitive therapy. All subjects also received instruction in programmed

practice self-exposure. Again these studies provide little evidence that adjunctive treatments such as relaxation or cognitive techniques increase the effectiveness of exposure whether therapist assisted or self-directed exposure. Modern proponents of cognitive therapy dismiss these early studies suggesting that the cognitive therapies employed were "...contrived and restricted variants of cognitive therapy procedures which bear little resemblance to the actual practice of cognitive therapy" (Clark & Beck 1988 p382).

1.8.2.4 Cognitive Behaviour Therapy for Panic

It appears that the noteworthy but limited gains achieved by exposure in vivo are not significantly enhanced by additional procedures. It has been suggested (Barlow 1988, McNally 1994) that both situations, the limited exposure gains and the ineffectiveness of adjunctive treatments, may be due to the fact that none of these treatment techniques directly target panic attacks. Indeed the early studies failed to measure panic at all. This is perhaps surprising given that the relevance of panic attacks to treatment outcome was recognised very early in the development of psychological treatments for agoraphobia. Gelder & Marks (1966) observed that exposure based treatment gains could be undone by a single panic attack and argued that "unless behaviour therapy can treat these apparently unexplained panic attacks little progress will be made" (Gelder & Marks 1966 p317). It has taken some considerable time for clinical psychology to live up to this prescient challenge, but it has recently done so with the development of cognitive and cognitive-behavioural treatments targeted specifically on panic attacks. These cognitive behaviour therapies developed in a number of centres from a variety of theoretical foundations, but share many overlapping features (Margraf et al 1993). As previously for therapies adjunctive to exposure the targets of cognitive behaviour therapy can be conceptualised as the disturbances to the cognitive, behavioural, and physiological systems caused this time by panic attacks. Thus comprehensive cognitive behaviour therapies such as Clark and Beck's Cognitive Therapy (Beck 1988, Clark 1988) or Barlow's Panic Control Treatment (Barlow & Cerny 1988) will include techniques designed to address disturbances in each of these systems. Taking each in turn, the classic cognitive model of panic (Clark 1986, 1988, Beck 1988) argues that panic attacks result from the catastrophic misinterpretation of bodily sensations, usually

those of anxiety. Thus the panic patient in a stressful situation will become mildly anxious, will identify the normal physiological arousal attendant on such anxiety but crucially will misinterpret this as being much more dangerous than it truly is, this causing more anxiety, further misinterpretation and so on. The cognitive model of panic further asserts that panic patients have an enduring tendency to misinterpret physical sensations in a catastrophic manner. This makes them acutely sensitive to any untoward or unexpected physiological arousal and vulnerable to further panic attacks. Treatments based on this model emphasise the identification and alteration of maladaptive catastrophic cognitions through Socratic discussion and also behavioural experiments. The latter usually take place in vivo and involve the attempted alteration of panic and anxiety driven thoughts and actions in anxiety provoking situations. The treatment therefor includes a large exposure based element. Patterns of misinterpretation can also be altered by the provision of accurate educational information on panic attacks. Indeed some have argued that this educational component of treatment is a crucial active ingredient in treatment (Shear et al 1994).

Behavioural components of treatment have included classic in vivo exposure for patients with obvious agoraphobic avoidance. This technique is not useful for patients with little or no agoraphobic avoidance where there are no avoided situations to form the basis of an exposure programme. Recognising that it is the sensations of panic as much as the situations in which they occur that patients attempt to avoid, Barlow and colleagues developed the concept of interoceptive exposure (Barlow 1988, Barlow & Cerny 1988). Interoceptive exposure consists of exposing the patient to the physical sensations of panic attacks either by their experiencing real panic attacks or by simulating the sensations via techniques such as chair spinning, vigorous exercise, straw breathing and so forth. During the interoceptive exposure the patient will be instructed not to avoid or attempt to ameliorate the sensations they experience. There are several suggested mechanisms for the effectiveness of interoceptive exposure, from a conditioning based extinction procedure through a cognitive explanation that the exposure to the sensations disconfirms patients catastrophic cognitions to a more behaviourally based explanation advanced by Barlow (Barlow 1988, Zinbarg et al 1992). Barlow (1988) argues that although anxiety and panic have traditionally been viewed as emotions

comprising characteristic patterns of physiological arousal and subjective cognitions, emotion theorists (Izard & Blumberg 1985, Izard 1993, Lang 1985, 1988) have long recognised that emotions are primarily action tendencies. Thus the avoidance behaviours and safety behaviours (Salkovskis et al 1996) characteristic of panic patients are not seen as a response to the panic attack but as a defining and central feature of it. Barlow (1988) further argues that action tendencies are one of the essential targets of change in the treatment of panic attacks and that " the crucial function of exposure (both in vivo and interoceptive), instead of facilitating extinction, is to prevent the action tendencies associated with fear and anxiety" (Barlow 1988 p311 parentheses added). Thus the potent ingredient in exposure is the alteration of what patients actually do rather than what they think. There have been as yet no controlled experimental investigations of this difference in emphasis from the classic cognitive model of panic.

Techniques focusing on the reduction of physiological arousal have also been developed and deployed in cognitive behavioural treatments for panic disorder. Recognising the limitations of traditional relaxation training Ost (1988) developed Applied Relaxation as a more potent alternative. Patients first learn progressive relaxation skills and then apply these in vivo in real anxiogenic situations in an attempt to prevent their anxiety spiralling into panic. This has been found to be an effective treatment technique that again includes the essential elements of in vivo practice and alteration of anxiety driven response. The other arousal reduction technique commonly employed in cognitive behavioural treatments is breathing retraining. This technique derived from the suggestion that panic attacks arise from a habit of chronic hyperventilation and are the physiological result of changes in pressure of carbon dioxide (pCO2) in blood. A treatment technique known as respiratory control (Clark et al 1985) was developed. This involved the deliberate provocation of symptoms via voluntary hyperventilation, discussion of the similarity between these sensations and those experienced during panic attacks and attribution of the panic symptoms to overbreathing, and finally, and importantly, training in controlled breathing techniques. Uncontrolled studies have suggested the efficacy of breathing control techniques (Clark et al 1985, Salkovskis et al 1986) but there is considerable controversy as to the accuracy of the underlying model and the suggested link between panic attacks and changes in pCO2. Garssen and colleagues

(Garssen et al 1992) in a critical review of the area found little evidence which supported a true hyperventilation model of panic and characterised breathing retraining as a "rational placebo" which exerts a therapeutic effect due to distraction effects and the provision of a sense of control rather than correction of hyperventilation induced decreases in pCO2. Most cognitive or cognitive behavioural therapies will employ at least some of the treatment techniques outlined above. These packages have proved highly effective in clinical use with reviews (McNally 1990, Chambless & Gillis 1993, Margraf et al 1993, Gould et al 1995) reporting substantial proportions of patients free of panic attacks post treatment and impressive reductions in generalised anxiety and avoidance.

1.8.3 Comparative Outcome Studies

The foregoing discussion has outlined the parallel development of pharmacological and psychological treatments for panic disorder. These developments have occurred for the most part separately with more rivalry than co-operation between the competing schools. This is also reflected in reviews of treatment outcome studies of either pharmacological or psychological treatments. Reviews are often conducted on only pharmacological (Judd et al 1990, Lydiard et al 1996), or only psychological (McNally 1990, Brown & Schulberg 1995) treatments, by practitioners of those treatments. It is not surprising that these reviews generally produce positive endorsements for the treatment type studied.

Some theorists have advocated combined pharmacological and psychological treatments (Telch 1988, Telch & Lucas 1994), and thus the consideration of relative efficacy inevitably arises. Given an extensive literature of variable quality on both the pharmacological and psychological treatment of panic disorder, the intending reviewer is faced with a daunting task. Comparisons between studies must be made not only both within the pharmacological and psychological treatment domains, but also between these two differing treatment types. Such comparisons may be difficult due to variations in basic study methodology such as differences in sample selection, outcome variables, control groups, and response rates. Despite these difficulties Clum (1989) undertook a comparative review of treatment efficacy of pharmacological and psychological treatments. This large scale review estimated the relative efficacies of pharmacological and psychological treatments on the basis of

three criteria; drop-out rates, treatment outcome rates, and relapse rates. Results from this review were complex but some general conclusions were drawn. Firstly, patients with panic disorder with agoraphobia showed poorer outcome than those with panic disorder without agoraphobia. Secondly, drop out rates were higher for the pharmacological interventions, especially antidepressants than for psychological treatments. Thirdly psychological treatments and high potency benzodiazepines showed the best outcomes, and lastly, psychological treatments had the lowest relapse rates. Considering all of these criteria Clum (1989) concluded that psychological treatments were superior to pharmacological treatments for panic disorder. These important findings should be considered with some caution however (Clum et al 1993). The review did not employ any method of weighting studies in the consideration of their outcome results. Thus, studies of vastly differing scientific rigour were afforded equal consideration in the review. It is clear that some method of facilitating the review and assessment of the literature on pharmacological and psychological treatments for panic disorder is required.

1.8.3.1. Meta Analysis

Meta analysis is the main method that has been employed to make sense of the large and variable treatment outcome literature for panic disorder. These techniques score over traditional reviews in that they yield standardised scores (known as effect sizes) for each treatment, facilitating comparisons between studies employing differing methodologies. Effect sizes can be calculated as either within treatment effect sizes (a), or between treatment effect sizes (b). Both are outlined below.

(a) Within Treatment Effect Size $\frac{Xp - Xpt}{SDp}$

Xp = pre-treatment group mean
Xpt = post-treatment group mean
SDp = pre-treatment standard deviation

(b) Between Treatment Effect Size $\frac{Xt - Xc}{SDc}$

Xt = post-treatment index group mean

Xc = post treatment control group mean

SDc = post treatment control group standard deviation

Other methods for the calculation of effect sizes using either the t or F statistic can also be employed for those studies where insufficient information is provided to permit the usual effect size calculations.

Five reviews of the panic disorder literature have employed meta-analytic procedures. Two of these reviewed only either pharmacological (Wilkinson et al 1991) or psychological (Chambless & Gillis 1993) treatments, and thus contribute little further to the important debate on the relative efficacy of these two treatment types. The other three reviews (Clum et al 1993, Gould et al 1995, Van Balkom et al 1995) assessed the relative efficacy of both pharmacological and psychological treatments and are therefor of considerable relevance to the current discussion. The first major meta-analytic review (Clum et al 1993) was designed and conducted specifically to overcome the problems noted with Clum's earlier non meta-analytic review (Clum 1989). The review examined 29 studies published between January 1964 and January 1990 which had a valid control group and could thus be subjected to meta analysis. Results from Clum et al's analysis suggested that the greatest efficacy was associated with cognitive panic management treatments and exposure based treatments, followed by the combination of exposure based treatments plus medication, antidepressant medications and finally high potency benzodiazepines and other medications. Clum et al (1993) also examined other variables that were hypothesised to affect the effect size of interventions, presence of agoraphobia, duration of the disorder, type of control group, and type of outcome variable examined. Presence of agoraphobia and duration of disorder were not significantly related to outcome. Treatment effects were evident across a range of outcome variables in both pharmacological and psychological treatments. Regarding type of control group, the use of exposure as a control comparison was associated with smaller effect size than were comparisons with other controls such as drug placebo,

psychological placebo (e.g. therapist contact), or relaxation groups. This is entirely in keeping with the finding already discussed that exposure functions as an effective treatment in its own right. Clum et al's (1993) review was unable to comment on the more recently developed cognitive behavioural treatments published since January 1990, or the recent studies on the SSRI antidepressants, or indeed on studies investigating their combined use. In an attempt to update the findings of Clum et al (1993), Gould et al (1995) conducted a further meta analysis on an expanded and updated sample of 43 studies of pharmacological, psychological or combined treatment outcome published between 1974 and March 1994. Effect sizes were averaged across treatment types. This meta analysis yielded the highest mean effect sizes for cognitive behavioural treatments (ES = 0.68) relative to pharmacological treatments (ES = 0.47) and combination treatments (ES = 0.56). Within cognitive behavioural treatments, studies that combined cognitive restructuring with interoceptive exposure yielded the strongest effect size (ES = 0.88). For pharmacological treatments, there was no significant difference between antidepressants (ES = 0.55) and benzodiazepines (ES = 0.40). Cognitive behavioural treatments also showed the smallest attrition rates compared to pharmacological and combined treatments. This appears at face value to be a resounding endorsement of psychological treatments for panic disorder, particularly cognitive behaviour therapy including cognitive restructuring and interoceptive exposure. Whilst Gould et al (1995) suggest that their meta analytic method provides a viable method "to adequately assess the relative effectiveness of pharmacotherapy, cognitive behavioural and combination treatments" (Gould et al 1995 p823), they nonetheless counsel some caution in the interpretation of their findings. Firstly they note that very few studies have investigated the efficacy of treatments combining medications with the new generation of potent cognitive behaviour therapies, and in addition they were unable to include in their analysis any of the recent studies on the SSRI antidepressants although they acknowledge the emerging consensus in psychopharmacology recognising the SSRIs as the pharmacological treatment of choice for panic disorder. The third meta analytic review (Van Balkom et al 1995) was conducted on 25 studies comparing pharmacological and psychological treatments for panic disorder published between 1964 and 1993. This review analysed a smaller sample of studies than the Gould et al (1995) review, as only

studies including within study comparisons of pharmacological and psychological treatments were included. This was reasoned to be a more controlled comparison than those made between studies in the other meta analyses. Van Balkom et al (1995) reached similar conclusions to the previous reviews regarding the comparative efficacies of pharmacological and psychological treatments for panic disorder and agoraphobia. Whilst Van Balkom et al's (1995) method of utilising only within study comparisons is a more controlled methodology than previous studies there are still problems with it. These more broad-based criticisms apply to the meta analytic method in general. There is a consistent difference between pharmacological and psychological studies in the choice of control groups against which target treatments are compared. Pharmacological studies tend to use drug placebo control groups whereas psychological studies have tended to use no treatment or waiting list controls. There is an obvious difference in the potential therapeutic potency of these two control groups that will tend to favour psychological treatments. That is, it is potentially easier for a psychological treatment to "beat" a no treatment control than it is for a pharmacological treatment to show efficacy against a drug placebo group. Thus the comparisons within a meta analysis may not be evenly weighted. Furthermore as it is the outcome data from each individual study which forms the basis of the meta analysis the claim that meta analysis permits the researcher to rise above the mundane consideration of individual study methodology is perhaps overstated. The position is exemplified by Gould et al who state "our conclusions are necessarily specific to the conditions under which well controlled studies are conducted. ..... Nonetheless we see no compelling evidence to lead us to doubt the validity of the results obtained in this meta analysis." (Gould et al 1995 p840). A cogent example of an area where concern and doubt remain is that relating to treatment outcome results for psychological treatments used alone. Outcome effect sizes are quoted for psychological treatments used alone, yet in many outcome studies of psychological treatments patients continued to take concurrent psychotropic medications (Power & Sharp 1995). In Gould et al's (1995) meta analysis, for example, of a total of 19 studies investigating psychological treatments supposedly used alone, only 5 studies required patients to discontinue concurrent psychotropic medications for the duration of the study. This represents a major confound in the data from such studies and the meta analyses derived from this data

are similarly suspect. This is only one example of potential methodological shortcomings in treatment outcome research, both pharmacological and psychological. A more fruitful approach to rectifying such methodological problems may be to attempt to irradicate them at source rather than compensate for them later. In other words whilst a useful indicative tool, meta analysis is no substitute for adequate study design in the first place. For any researcher wishing to compare pharmacological with psychological treatments for panic disorder, the most useful initial route to take would be to do so within the framework of a coherent single study design ensuring that such a design rectifies any inadequacies in previous study design. Given that the meta analytic studies discussed here were unable to comment on the relative efficacies of the currently recommended pharmacological and psychological treatments for panic disorder and agoraphobia, namely the SSRI antidepressants and the newer cognitive behaviour therapies, this would seem a reasonable place to start. A useful next step would therefor be a controlled comparison of the relative and combined efficacies of these two treatments. If such a study is to attempt to rectify some of the methodological problems of previous treatment outcome research, the first requirement will be a substantial consideration of treatment outcome methodology, its problems and potential solutions to them. This forms the basis of Chapter 2 of this thesis.

CHAPTER 2 A REVIEW OF TREATMENT OUTCOME STUDY METHODOLOGY

2.1 Introduction

Panic disorder with or without agoraphobia is a prevalent and clinically demanding condition, with efficacy claimed for both pharmacological and psychological treatments (Wolfe & Maser 1994). Treatment outcome studies have been conducted by either pharmacologically or psychologically oriented researchers with study designs and subsequent conclusions often reflecting the allegiances of the researchers (Kendal & Lipmann 1991). The overall impression in this area remains one of confusion and conflict as to preferred treatment, resulting in considerable debate over methodology and study design. The debate has touched on specific issues such as concomitant treatments (Power & Sharp 1995, Otto et al 1996), and on the broader issue of methodology in studies assessing the relative and combined merits of pharmacological and psychological treatments (Jacobson & Hollon 1996, Klein 1996). Other researchers have attempted to circumvent the problems of differing study designs by employing review techniques such as meta analysis (Gould et al 1995). These meta analytic techniques, based on calculations of effect sizes, are useful indications of relative treatment efficacy when reviewing results from varying study designs. They are not, however, a replacement for adequate study design in the first place, and if study design is flawed, the results from any meta analysis are compromised.

Study design is not only defined, and indeed constrained, by the conflicting demands of partisan researchers, but also more importantly by its ultimate task of informing clinical practice. There is little point in constructing an elegant study encompassing the most sensitive of scientific controls if the treatments employed, or populations studied become so restricted that they are no longer representative of wider clinical practice. Any study of either the relative or combined efficacies of pharmacological or psychological treatments must therefor attempt to balance and reconcile the demands and methodologies of both approaches. Furthermore, the study design must also be as representative as possible of wider clinical practice if results are to be of any practical value. Given the difficulty of this task it is no surprise that previous methodologies have been found wanting, to the extent that some have decried research in the area as "....a waste of time and money,...." (Klein 1996 p86).

The aim in this chapter is to review the methodologies of treatment outcome studies in panic disorder and agoraphobia, covering firstly psychological treatments, and secondly studies where psychological treatments were compared and/or combined with pharmacological treatments. The review aims to highlight the main areas where the competing demands of research design and clinical applicability lead to dilemmas for the researcher. Attempts to overcome these dilemmas will be described and alternative solutions suggested where appropriate. Given the nature of the task the review will be illustrative rather than exhaustive, aiming to produce a set of compromises in research design for use in future treatment outcome studies. Particular emphasis will be given to the design of studies comparing the relative and combined efficacies of both pharmacological and psychological treatments.

For psychological treatments, literature search revealed 41 studies published since 1980 that investigated the treatment efficacy of one or more psychological treatments. Of the 41 studies 5 were reanalyses of previous studies or specific analyses of previous studies not directly related to treatment outcome. This review is therefor based upon the 36 core studies of this set listed in Table 2.1 (studies are subsequently referred to in text by number as illustrated in Table 2.1).

For studies investigating pharmacological vs. psychological treatments, literature search revealed 24 studies published since 1980 that compared the efficacies of drug and psychological treatments employed either as individual or combined treatments. Of these 24 studies, 4 were reanalyses of previous studies, or continued analyses of expanded data sets. This review is therefor based upon the 20 core studies of this set which are enumerated and listed in Table 2.2 (studies are subsequently referred to in text by number as illustrated in Table 2.2).

Table 2.1 Psychological Treatment Studies Included In Review

AUTHORS	TREATMENT COMPARISONS N =	STUDY SETTING REFERRAL SOURCE	OUTCOME
1. Benjamin & Kincey (1982)	BT = 9	Hospital In-Patients Referral source-Unkn	--------
2. Chambless et al (1982)	FL = 8 FL + Brev = 7 Rel = 6	Hospital clinic Self referred	FL > FL + Brev + Rel

3. Emmelkamp & Mersch (1982)	Exp = 9 CT = 9 Exp + CT = 9	Hospital clinic Referral source-Unkn	Exp = Exp + CT > CT
4. Emmelkamp et al (1983)	Exp = 7 AT = 7 AT + Exp = 7	Hospital clinic Referral source- Unkn	AT + Exp = Exp > AT
5. Mavissakalian et al (1983)	SST + PP = 12 PI + PP = 12	Hospital clinic Referral source- Unkn	SST + PP = PI + PP
6. Williams & Rappoport (1983)	Exp = 10 Exp + CT = 10	University clinic Self referred via advert	Exp = Exp + CT
7. Waddell et al (1984)	WL- CT- Rel + CT = 3	University clinic Referral source- Unkn	-------
8. Ost et al (1984)	Exp = 20 AR = 20	Hospital clinic Medical referral	Exp = AR
9. Alstrom et al (1984)	Inf = PP = 19 Inf + Exp = 11 Inf = Pther = 14 Inf + Rel = 17	University clinic Psychiatric referral	Inf + PP = Inf + Exp = Inf + Pther = Inf + Rel
10. Gittlin et al (1985)	BT = 11	Hospital clinic Referral source- Unkn	-------
11. Clark et al (1985)	BRT = 18	Hospital clinic Psychiatrist and GP referral	-------
12. Michelson et al (1985)	PI + PP = 10 Exp + PP = 11 Rel + PP = 10	Hospital clinic Referral source- Unkn	Exp + PP > Rel + PP >PI + PP
13. Burns et al (1986)	Exp = 20	Hospital clinic Referral source- Unkn	-------
14. Himadi et al (1986)	CT + PP + Spouse =28 CT + PP = 14	University clinic Referral source- Unkn	CT + PP + Spouse = CT + PP
15. Marchione et al (1987)	CT + Exp + PP = Unkn Rel + Exp + PP= Unkn Exp + PP = Unkn Total n = 14	Hospital clinic Referral source- Unkn	CT + Exp + PP = Rel + Exp + PP > Exp + PP
16. Ost et al (1988)	Rel = 8 AR = 8	Hospital clinic Psychiatrist and GP referral	AR > Rel

17. Craske et al (1989)	CT + PP + Spouse = 22	University clinic Referral source- Unkn	-------
18. Williams & Zane (1989)	GM = 15 Exp = 11 WL = 6	University clinic GP Referred and self referred via advert	GM > Exp > WL
19. Sokol et al (1989)	CT = 17	Hospital clinic Self referred	-------
20. Barlow et al (1989)	Exp + CT = 15 Rel = 10 Exp + CT + Rel =16 WL = 15	University clinic Psychiatrist and self referred	Exp + CT = Exp + CT + Rel > Rel > WL
21. Michelson et al (1990)	CBT = 10	University clinic Referral source- Unkn	-------
22. Welkowitz et al (1991)	CBT = 19	Hospital clinic Referral source- Unkn	-------
23. Shear et al (1991)	CBT = 23	Hospital clinic Referral source- Unkn	-------
24. Salkovskis et al (1991)	CT = 7	Hospital clinic Psychiatrist and GP referral	-------
25. Beck et al (1992)	CT = 17 Pther = 16	University clinic Referral source- Unkn	CT > Pther
26. Ost et al (1993)	AR = 15 CT = 15 Exp = 15	Hospital clinic Referral source- Unkn	Exp = AR > CT
27. Telch et al (1993)	CT = 34 WL = 33	University clinic Physician Psychiatrist and self referred	CT > WL
28. Shear et al (1994)	CBT = 24 NP = 21	University clinic Referral source- Unkn	CBT = NP
29. Beck et al (1994)	CT = 17 Rel = 19 MCC = 22	University clinic Self referred via advert	CT + Rel > MCC
30. Lidren et al (1994)	CBT = 12 Bib = 12 WL = 12	University clinic Physician referred and self referred via advert	CBT = Bib > WL

31. Cote e al (1994)	CBT = 10 RCCBT = 11	University clinic Psychiatrist GP and self referral	CBT = RCCBT
32. Craske et al (1995)	CBT = 16 NDT = 13	University clinic Self referred via advert	CBT > NDT
33. Williams & Falbo (1996)	CBT = 14 GM = 12 CBT + GM = 13 WL = 9	University clinic Self referred via advert	CBT = GM = CBT = GM > WL
34. Bouchard et al (1996)	Exp = 14 CT = 14	University clinic Psychiatrist GP and self referred	Exp = CT
35. Arntz & Van Den Hout (1996)	CT = 18 AR = 18 WL = 18	University clinic Psychiatrist referred	CT > AR > WL
36. Hecker et al (1996)	CBT = 5 SGCBT = 8	University clinic Physician Psychiatrist and self referred	CBT = SGCBT

KEY: Unkn = unknown, Brev = Brevital, BT = Behaviour Therapy, FL = Flooding, Rel = Relaxation, Exp = Therapist Guided Exposure, CT = Cognitive Therapy, CBT = Cognitive Behaviour Therapy, AT = Assertiveness Training, SST = Self Statement Training, PP = Programmed Practice Self Directed Exposure, PI = Paradoxical Intention, WL = Waiting List Control, AR = Applied Relaxation, Inf = Information, Pther = Dynamic/Supportive Psychotherapy, BRT = Breathing Retraining, GM = Guided Mastery, NP = Non-prescriptive Treatment, MCC = Minimum Contact Control, Bib = Bibliotherapy, RCCBT = Reduced Contact CBT, NDT = Non-directive Therapy, SGCBT = Self Guided CBT.

Table 2.2 Psychological vs. Pharmacological Treatment Studies Included In Review

AUTHORS	TREATMENT COMPARISONS N =	STUDY SETTING REFERRAL SOURCE	OUTCOME
1. Zitrin et al (1980)	Imip + Exp = 41 Plac + Exp = 35	Hospital clinic Medical/ Psychiatric referral	Imip + Exp > Plac + Exp
2. Barr-Taylor et al (1982)	Diaz = 8 Plac = 10 Rel = 10 W/L Control = 11	Hospital clinic Self referred via advert	Diaz = Rel > Plac > W/L

3. Zitrin et al (1983)	Imip + BT = 56 Plac + BT = 57 Imip + Pther = 58	Hospital clinic self referred	Imip + BT > Plac + BT = Imip + pther
4. Marks et al (1983)	Imip + Exp + PP = 12 Imip + Rel + PP =11 Plac + Exp + PP = 10 Plac + Rel + PP = 12	Hospital clinic Referral source-Unkn	Imip + Exp + PP = Plac + Exp + PP > Imip + Rel + PP = Plac + Rel + PP
5. Mavissakalian et al (1983)	Imip = 7 Imip + BT = 8	Hospital clinic Referral source-Unkn	Imip + BT > Imip
6. Telch et al (1985)	Imip + Exp = 12 Plac + Exp = 13 Imip = No Exp = 12	University clinic Referral source-Unkn	Imip + Exp > Plac + Exp = Imip + No Exp
7. Michelson & Mavissakalian (1985)	Imip + Exp + PP = 14 Imip + PP = 17 Plac + Exp + PP = 17 Plac + PP =14	University/ hospital clinic Referral source-Unkn	Imip + Exp + PP = Imip + PP = Plac + Exp + PP > Plac + PP
8. Charney et al (1986)	Imip + BT = 24 Traz + BT = 27 Alpraz + BT = 23	Hospital clinic Referral source-Unkn	Imip + BT = Alpraz + BT > Traz + BT
9. Tobena et al (1990)	Alpraz + BT = 32	University clinic Self referred via advert	———
10. Klosko et al (1990)	Alpraz = 16 CBT = 15 Plac = 11 W/L Control = 15	University clinic self referred	CBT = Alpraz > W/L, CBT > Plac, Alpraz = Plac
11. Mavissakalian (1990)	Imip + Exp = 38	Hospital clinic Referral source-Unkn	———
12. Fahy et al (1992)	Clomip + CBT = 18 Lofep + CBT = 24 Plac + CBT = 24	Hospital clinic GP Referral	Clomip + CBT = Lofep + CBT > Plac + CBT
13. Black et al (1993a)	Fluvox = 21 Plac = 18 CBT = 16	Hospital clinic Physician referred and self referred via advert	Fluvox > CBT + Plac

14. Marks et al (1993)	Alpraz + Exp = 34 Alpraz + Rel = 34 Plac + Exp = 30 Plac + Rel = 31	Hospital clinic Physician referred and self referred	Alpraz + Exp = Plac + Exp > Alpraz + Rel = Plac + Rel
15. Clark et al (1994)	CT + PP = 16 AR + PP = 16 Imip + PP = 16 W/L Control = 16	Hospital clinic Psychiatrist GP and Psychologist referred	CT + PP > AR + PP = Imip + PP > W/L
16. Hegel et al (1994)	Alpraz + CBT = 22	University clinic Physician referred	———
17. Cottraux et al (1995)	Busp + CBT = 21 Plac + CBT = 27	University clinic Referral source-Unkn	Busp + CBT > Plac + CBT
18. Oehrberg et al (1995)	Parox + CBT = 55 Plac + CBT = 52	Setting-Unkn Referral source-Unkn	Parox + CBT >Plac + CBT
19. De Beurs et al (1995)	Fluvox + Exp = 19 Plac + Exp = 19 PM + Exp = 20 Exp = 18	University clinic GP Referred and Self referred	Fluvox +Exp>Plac + Exp = PM + Exp = Exp
20. Sharp et al (1996)	Fluvox = 29 Plac = 28 CBT = 30 Fluvox + CBT= 29 Plac + CBT = 33	Primary care GP referred	Fluvox = CBT = Fluvox + CBT = Plac + CBT > Plac

KEY: Unkn = Unknown, Imip = Imipramine, Traz = Trazodone, Alpraz = Alprazolam, Clomip = Clomipramine, Lofep = Lofepramine, Busp = Buspar, Parox = Paroxetine, Fluvox = Fluvoxamine. CT = Cognitive Therapy, CBT = Cognitive Behaviour Therapy, BT = Behaviour Therapy, Exp = Exposure, Rel = Relaxation, W/L = Waiting List, Pther = Psychotherapy, PP = Programmed practice self directed exposure, PM = Panic Management.

2.2 Overall Study Design

The dilemma in this area is that the design of any study must permit an accurate and controlled investigation of the treatments studied, whilst controlling for as many potentially confounding factors as possible. For the results of such studies to be of

value, however, the delivery of the treatments employed must be as close as possible to their use in wider clinical practice.

The design of a study may also be influenced by the purpose of the study. A distinction has been drawn (Schwartz & Lellouch 1967) between studies conducted simply to inform or audit normal clinical practice, i.e. pragmatic designs, and those designed to acquire scientific information, i.e. explanatory designs. The rigour of scientific control differs between pragmatic and explanatory designs with more control being required in the latter to ensure that conclusions are not drawn from data confounded by uncontrolled artefact. It is likely that most study designs will reflect a careful balance of these design types.

2.2.1 Psychological Treatment Studies

Of the 36 studies reviewed (Table 2.1), 11 are open trials of a single psychological treatment. The open trial design lends itself to maximising the similarity between research treatments and wider clinical practice but represents the minimum of scientific control. Other researchers have employed waiting list or no-treatment groups (Table 2.1. 18,20,27,33,35). This allows researchers to calibrate the effectiveness of the target treatment against the established effect of no treatment, but does not allow a conclusion that it is the treatment itself that is effective as opposed to simple contact with a therapist or other secondary factors. To resolve this problem, some have recommended the use of psychological placebo treatments (Marks et al 1993). Psychological placebo treatments are rarely used in psychological treatment outcome studies as their applicability and validity have been questioned (Parloff 1986). It is indeed difficult to conceive of a psychological intervention which would fulfil the criteria of being therapeutically inert whilst at the same time retaining credible face validity.

A minimum standard design for psychological treatment studies would be to employ a no treatment or waiting list control, or the use of a placebo psychological treatment condition. Given the controversy over placebo psychological treatments, a compromise strategy with more direct relevance to wider clinical practice would be to ensure that any psychological treatment under investigation is compared with the most widely used clinical alternative as well as a no treatment condition. Studies have compared psychological treatments, usually cognitive therapy or cognitive

behaviour therapy with other psychotherapies e.g. supportive psychotherapy (Table 2.1. 19), or non-prescriptive therapy (Table 2.1. 28). If it is suggested that psychological treatments should be compared with the most widely used clinical alternative, however, then this will usually mean comparison with a pharmacological treatment. This will involve an increase in the complexity of study design and recognition and accommodation of the requirements of pharmacological study design.

2.2.2 Psychological vs. Pharmacological Treatment Studies

A major requirement of any study investigating a drug treatment is the use of a pill placebo group. The pill placebo group permits a control for the drug responsiveness of the sample. When using drugs of proven efficacy for panic disorder, such as imipramine or alprazolam, the lack of a drug vs. pill placebo difference would indicate that caution should be taken in interpreting results. Klein (1996) argues that the lack of a drug vs. pill placebo difference in such circumstances indicates that the sample under study is atypically unresponsive to drug treatment, unrepresentative of the wider clinical population and that results from such samples should be discounted. Others (McNally 1996, Jacobson & Hollon 1996), suggest that lack of response to drug treatment is only one possible reason for finding a lack of drug vs. pill placebo difference, which could plausibly be due to equal ineffectiveness, or equal effectiveness of drug and pill placebo treatments. Nevertheless, the inclusion of both a drug and a pill placebo group are required for any research design to untangle these potential effects. The pill placebo group also controls for other non-drug effects such as basic therapist contact or attention effects. Such factors may be powerful in panic disorder (Fossey & Lydiard 1990, Mellergard & Rosenberg 1990). Of the 20 studies reviewed (Table 2.2) 14 employed pill placebo groups with only one study (Table 2.2. 10) failing to find a drug vs. pill placebo difference. Of the 6 studies which did not employ a pill placebo, 3 were open trials of combined pharmacological plus psychological treatments, (Table 2.2. 9,11,16). Open trials of combined drug + psychological treatments cannot provide information on the relative merits of each treatment used alone, or address the issue of drug responsiveness of the sample. The other 3 studies (Table 2.2. 5,8,15) all attempted drug versus psychological treatment comparisons, or comparisons of differing drug +

psychological treatment combinations (Table 2.2. 5,8) without employing pill placebo groups. This omission makes these studies more difficult to interpret. The inclusion of pill placebo controls satisfies the demands of good pharmacological research design, and is to be recommended as a design standard. A further design standard to be considered refers to the psychological treatment element of drug vs. psychological treatment comparisons. Previous studies have employed a wide variety of designs from simple between group comparisons of various drug + psychological treatment conditions (Table 2.2. 17,18) to more complex 2 x 2 designs comparing drug vs. pill placebo with exposure vs. relaxation. These designs have four treatment groups; drug + exposure, drug + relaxation, pill placebo + exposure, and pill placebo + relaxation. The essence of this design rests in the assumption that relaxation operates as a "placebo" psychological treatment, and thus both drug and psychological treatments are assumed to be represented by an active and a placebo index (Table 2.2. 4,14). As already mentioned there is disagreement over the validity of psychological placebos in general (Parloff 1986), and relaxation treatments as psychological placebos in particular (Ost et al 1993). Also, as no treatment is represented independently used alone within these designs, such studies do not permit a calibration of the relative efficacies of the drug and psychological treatments.

Only five studies have employed a psychological treatment alone condition (Table 2.2. 10,13,15,19,20). All other studies have assumed a pill placebo + psychological treatment to be equivalent to a psychological treatment alone condition and have employed only the former. Lack of psychological treatment alone conditions in previous studies is a serious design flaw. In four of the five studies which do include a psychological treatment alone condition, three (Table 2.2. 10,13,15), do not include any combined treatment conditions, whilst the fourth (Table 2.2. 19), does not include a drug alone or a pill placebo alone condition. Thus in these four studies the definitive comparison of each treatment used alone and in combination is not possible.

Hollon & DeRubies (1981) argue that a minimum of 5 groups are required to adequately compare the relative and combined efficacies of a drug and a psychological treatment, namely; drug alone, pill placebo alone, drug + psychological treatment, pill placebo + psychological treatment, and psychological treatment alone.

This represents the minimum design standard for comparative studies. Only two studies, one recent (Table 2.2. 20), the other (Barlow 1994) ongoing, have used the five group design with panic disorder patients.

2.2.3 Design Solutions

The need for wider clinical application suggests that psychological treatments should be compared with the most widely used clinical alternative, i.e. pharmacological treatments. A consideration of the design of drug vs. psychological treatment studies suggests that any such comparison should be conducted within the framework of a five group study design. The adoption of this design standard is not without some cost. The immediate and obvious cost of this suggested solution to the dilemmas of study design is the increase in the number of study groups required in any comparison and the consequent increase in sample size required to ensure sufficient statistical power.

2.3 Definition/Classification of Sample

Once study design is established the next major stage in any research study is the definition of the patient group to be studied. Treatment outcome studies must employ a system whereby the group under study can be defined. Such a system should be described in sufficient detail to permit other researchers to replicate it. In wider clinical practice, however, patient groups are rarely well defined and typically show considerable co-morbidity and varying chronicity and severity. The dilemma for the researcher here rests in reconciling the requirement for definition and control in treatment research with the wider variability in presentation found in clinical practice.

2.3.1 Psychological Treatment Studies

Many studies make no mention of classificatory systems (Table 2.1. 1,3,4,6,8,9, 11,13,18) and comparisons with these studies are less reliable as a result. Other studies do use classification systems but do not describe the procedures employed for assessing patients against the criteria of the classificatory system (Table 2.1. 2,5,10,22, 24). Others have employed "semi-structured interviews" which are rarely available for inspection thus compromising replicability. Barlow (1989) argues that

the only acceptable method of classification is by standardised interview schedules based upon internationally accepted classificatory systems such as the ADIS-R (Di Nardo & Barlow 1988) or SCID (Spitzer et al 1988). Most of the more recent psychological treatment studies have used one of these methods (Table 2.1. 7,14,16,17,19,20,23,25-36).

A further problem as regards classification is the use of additional criteria above those of the standardised system. Some studies included moderate to severe agoraphobics in their samples (Table 2.1. 1-8,12,14,17,26,33), while others included patients with mild or no agoraphobic avoidance (Table 2.1. 7,10,16,18,23,25,35). Still others included a large proportion of agoraphobic subjects in the sample but did not define levels of severity of agoraphobic avoidance (Table 2.1. 9,11,13,15,19,22, 25,27,28,31,32,34,36). The exclusion of severe agoraphobics may bias the sample towards responsiveness (Clum 1989, Williams & Falbo 1996), giving an overly optimistic picture of the efficacy of psychological treatments.

Clinical samples can show considerable co-morbidity, particularly with regard to depression (Wittchen & Essau 1993). Although measures of depression are commonly employed as outcome measure, most studies of psychological treatments did not employ any controls for concurrent depression or make any mention of pre-treatment depression levels in their samples. Seven studies excluded subjects with major depression if this was judged to be the primary disorder (Table 2.1. 10,16,20, 26,30,31, 35), whilst a further 3 studies employed the stringent criterion of excluding any subjects who had any history of depressive disorder, including that prior to the onset of their panic disorder (Table 2.1. 5,12,21). The effect of this strict control on the representativeness of these samples is unknown. Patients with high levels of concurrent depression may be more treatment resistant (Wittchen & Essau 1993), thus a controlled investigation of the influence of depression levels on treatment outcome is required.

2.3.2 Psychological vs. Pharmacological Treatment Studies

Review of studies investigating psychological vs. pharmacological treatment studies revealed findings similar to those for psychological treatments alone. Less studies failed to use any recognised classificatory system (Table 2.2. 1,3), however many others did not specify any standardised or replicable procedures for assessing patients

against the criteria of the classificatory system employed (Table 2.2. 2-7,9,18,19). Others again employed "semi-structured interviews" (Table 2.2. 17,20). As with the psychological treatment studies, these were unavailable for inspection thus replicability was equally compromised. Most of the more recent studies in this group have employed recognised classificatory systems and standardised interview schedules such as the ADIS-R or SCID (Table 2.2. 10, 12-16). Regarding criteria over and above those of the standardised classificatory system, some studies have excluded severe agoraphobics from their samples (Table 2.2. 15,16), with the same implications for treatment responsiveness as before. Other additional criteria used include chronicity and severity (Table 2.2. 19,20), the effect of which on treatment responsiveness is unclear. These are issues worthy of increased attention.

Regarding depression, a larger proportion (9 out of 20) of the psychological vs. pharmacological treatment studies excluded patients suffering from concurrent major depression. Unfortunately, many of these studies did not state the explicit criteria on which such exclusions were made (Table 2.2. 4,5,7,10,12). Others have rectified this problem by excluding patients whose rated depression exceeds pre-determined levels on standardised rating scales (Table 2.2. 9,18,20). Such exclusions may nonetheless bias these samples towards treatment responsivity.

2.3.3 Design Solutions

How a research sample is defined has major ramifications for the representativeness of that sample and consequently the applicability of findings to wider clinical practice. The constitution of a sample may also have implications for treatment responsiveness. The use of recognised classificatory systems, standardised interviews and the investigation of and controls for the influence of co-morbid conditions would be important improvements, but would not completely resolve the initial dilemma. Any classification of a condition, by definition, restricts the number of patients who can be so classified. Thus any research sample will not wholly replicate the disorder as seen in wider clinical practice. Scientific rigour and replicability of research is inevitably traded against the representativeness of the sample, and to this extent the dilemma still stands. Further research effort should consider the areas where samples differ from the wider clinical population, and the ramifications of such differences.

The representativeness of the sample should also be borne in mind when interpreting results from any research study.

2.4 Definition of Treatment

Research treatments must be defined sufficiently to permit replication. Definition may cause problems if treatments are then unrepresentative of the treatments used in wider clinical practice. This is possibly a less convincing dilemma in that good clinical practice also requires well defined replicable treatments. Some of the flexibility in actually delivering treatments in wider clinical practice may, however, be lost in the more strictly controlled research setting.

2.4.1 Psychological Treatment Studies

Psychological treatments are complex to deliver and require detailed specification in a research protocol. A minimum specification of a psychological treatment would include the use of a treatment manual that details the essentials of the treatment in question (Barlow 1989). Several of the studies reviewed failed to use a treatment manual. Other studies have used a treatment manual (Table 2.1. 4,11,16,19,23,25,28, 36), although this may not be sufficient in itself as no further check was made to ensure that the directions of the manual were adhered to. The problem of definition of treatments may be resolved by the use of treatment manuals with checks on treatment integrity possibly by the use of audio or video recordings of treatment sessions as adopted by some studies (Table 2.1. 12,20,22,29,30,32-34).

2.4.2 Psychological vs. Pharmacological Treatment Studies

A noticeable difference exists between pharmacological and psychological treatments. The use of pharmacological treatments is generally well defined with the use of specified dosage ranges and schedules. Compliance with drug treatments is routinely assessed either by return pill count, or by blood screen. A different situation holds for the psychological treatments employed in comparative studies, which are more complex to deliver and require more detailed specification. Several studies failed to use treatment manuals (Table 2.2. 1-6,9,12,18), or used manuals but did not make any checks on the integrity of treatment delivery (Table 2.2. 4,11,13,16,17).

Only 5 of the 20 comparative studies reviewed used treatment manuals along with audio or video taped integrity checks (Table 2.2. 10,14,15,19,20).

2.4.3 Design Solutions

The resolution of this area requires the adequate specification of treatments, using treatment manuals for psychological treatments, with subsequent checks on treatment integrity possibly by the use of audio or video tapes of treatment sessions. These procedures undoubtedly enhance the replicability of treatments but nonetheless involve some cost. Specification of treatment procedures by the use of manuals may restrict some of the essential ingredients of treatment such as the quality of the therapist patient relationship or the ability of the treatment to accommodate and respond to variations in individual patients circumstances (Kendal & Lipman 1991). Also, audio or video taped integrity checks may exert a confounding influence on the sessions taped, rendering this an invalid reflection of the treatment as practised in wider clinical practice. This is a research topic in itself that is worthy of further investigation.

2.5 Therapist Contact

In normal clinical practice treatments vary between patients in the number of sessions given and the length of individual sessions, these factors reflecting the circumstances of individual patients. In treatment research, however, therapist contact must be controlled. In both within and between group comparisons, it is essential to be sure that differences in outcome are due to genuine differences between treatments and not to differences in the amount of therapist contact received. There is a clear dilemma over reconciling these obviously conflicting requirements. This is an example where the demands of research methodology must take precedence over those of clinical practice if study results are to have any explanatory value.

2.5.1 Psychological Treatment Studies

Several studies have failed to control for therapist contact within treatments with patients receiving differing numbers of sessions and amounts of therapist contact (Table 2.1. 1,7,10,23-25). Others attempt to control for therapist contact by ensuring

all subjects receive an equal number of treatment sessions (Table 2.1. 3,4,9,12,26). Thus in a study comparing a relaxation treatment with a therapist assisted graded exposure treatment, all patients are given exactly the same number of treatment sessions. The therapist contact element of the graded exposure is, however, reduced as treatment progresses. Thus, whilst all subjects receive an equal number of treatment sessions within this design, there is still considerable variation in actual therapist contact. Overall therapist contact is generally well controlled in outcome studies of psychological treatments with 20 of the 36 studies employing adequate balances for this factor.

2.5.2 Psychological vs. Pharmacological Treatment Studies

Therapist contact is of particular relevance to the comparison of pharmacological versus psychological treatments. In normal clinical practice there are usually large differences in the amount of therapist contact required to deliver drug treatment or psychological treatment. Differences in outcome between the two treatment types may simply reflect this substantial procedural difference. An explanatory research design must recognise and control this factor. Unfortunately some studies (Table 2.2. 5,6,15), do not address the issue while others attempt balance by ensuring that all subjects receive equal numbers of treatment sessions but fail to ensure that these are of equal duration (Table 2.2. 10,13). A more sophisticated attempt to balance therapist contact across groups was made in studies which employ a 2x2 design (Table 2.2. 4,7,14), where all patients in all four treatment groups received an equal number of sessions. To deal with the confounding effects of high levels of therapist contact during psychological treatment versus low levels of contact during drug treatment, an approach that balances for therapist contact across all treatments is required.

2.5.3 Design Solutions

The suggestion that all treatments in a comparative study should receive equal amounts of therapist contact is not difficult to accommodate within a comparison of psychological treatments. It is in the area of drug versus psychological treatment comparisons where there are substantial natural differences in therapist contact between the two treatment types that problems arise. In the later studies patients

allocated to drug alone or pill placebo alone conditions must be given the same amount of therapist contact as those in the psychological treatment groups. One possible means of achieving this the sessions for the drug and pill placebo alone groups focus on non-directive empathic reflection of patients problems with no active therapeutic advice being offered. This may at best represent only a partial solution to the problem, or at worst, no solution at all. It could be argued that therapist contact which involves empathic reflection may be therapeutically active (Rogers 1957) and thus an unsuitable analogue for simple therapist contact. Attempts made to date to balance for therapist contact using non directive empathic reflection (Power et al 1990a, Sharp et al 1996) may simply have introduced yet another confounding factor into such study designs rather than provide a solution. This observation notwithstanding, when comparing pharmacological versus psychological treatments, in an explanatory as opposed to a pragmatic design, the overall recommendation remains that therapist contact should be balanced between groups. This should take place within a five group framework where each treatment is represented both used alone and in combination. This method does have a major drawback in that with the balance for therapist contact included the drug alone groups (drug, and pill placebo alone) receive significantly more therapist contact than would be the case in wider clinical practice, thereby resulting in an ecologically invalid representation of drug alone treatments and possibly producing an over estimate of the effectiveness of drug treatments. In explanatory designs, if therapist contact is to be balanced across groups within a five group framework it would therefor seem necessary that a further two groups are run, these being drug + standard (i.e. shorter) contact and pill placebo + standard contact. In this way the contribution of the enhanced therapist contact can be calibrated. The strategy does have obvious costs, in that the number of study groups has now increased to a possible seven with the commensurate increase in number of subjects required per group. In order to assess whether such an increase in the complexity of study design is in fact necessary, research should be conducted comparing drug or pill placebo + standard contact versus drug or pill placebo + enhanced (i.e. balanced) therapist contact. Until results from such research are available the dilemma over controls for therapist contact remains.

2.6 Control For Concurrent Treatments

In normal clinical practice patients undergo both drug and psychological treatments whilst receiving other treatments. An explanatory research design demands that patients be free from concurrent treatments in order that target treatments can be properly assessed. The dilemma here rests in the conflicting demands of scientific control and wider clinical practice. This is an area of considerable importance which has a direct impact on the validity of study results, and where the demands of research methodology must take precedence if results are to have any explanatory meaning. The problem is easily resolved in practical terms by simply prohibiting the use of concurrent psychotropic medications and concurrent psychological treatments.

2.6.1 Psychological Treatment Studies

Concurrent psychotropic medication is unfortunately rarely controlled in studies of psychological treatments with 29 of the 36 studies either failing to mention concurrent psychotropic drugs, or employing inadequate controls. This has been suggested to be a failing in research design (Beck et al 1994, Power & Sharp 1995), although others have suggested that outcome results are not affected (Otto et al 1996). Controls usually consist of requiring patients to maintain the dose of concurrent psychotropic medication at a constant level throughout the study period, assuming that the influence of the drug on the outcome of the psychological treatment under investigation will thus be controlled. This does not take account of the possibility of medication by psychological treatment interaction effects, nor control for differential medication effects or for actual medication dosage. Some studies have attempted post hoc controls for concurrent psychotropic medication by comparing the outcomes of those patients taking psychotropic medication with those who were not (eg Table 2.1. 27) and finding no differences between the two groups. Limited sample sizes and the dangers of interpreting findings for the null hypothesis, suggest that these results be approached with caution.

Some studies (Table 2.1. 5,6,35), employed partial controls for concurrent psychotropics by prohibiting the use of certain classes of psychotropics, usually antidepressants, whilst permitting the continued use of others, e.g. benzodiazepines.

Such partial control procedures are hard to justify. Others (Table 2.1. 3,4,12,15, 21, 28, 29), prohibited the use of concurrent psychotropic medication but employed variable wash-out periods from 0 days (Table 2.1. 3,4), to 14 days (Table 2.1. 12,15,21,23,29). The surreptitious use of psychotropic medications has also been identified (Clark et al 1990). Surprisingly, only one study has employed checks on surreptitious medication use by using urine screens (Table 2.1. 28).

Regarding concurrent psychological treatments, the majority of psychological treatment studies (17 of 36) make no mention of concurrent psychological treatment. Other studies fail to control for concurrent psychological treatment as a result of basic study design (Table 2.1. 4,9,12,15,26), in that treatment groups were given programmed practice self exposure instructions in addition to the research treatment. Programmed practice has been shown to be an effective treatment in its own right (Mathews et al 1981) and is suggested to be a common active ingredient in many psychological treatments (Al-Kubaisy et al 1992). Thus treatment effects are confounded rendering these studies uninterpretable. Another study permitted concurrent psychological treatments if these were not directly targeting patients panic disorder (Table 2.1. 20). Knowledge of the active ingredients in any psychological treatment is not sufficiently advanced to permit such a control to be used with any confidence. Five studies prohibited concurrent psychological treatments during the study period (Table 2.1. 4,28,33,34,35). Controls for both concurrent psychotropic medication and concurrent psychological treatments were employed in only two studies (Table 2.1. 4,28).

2.6.2 Psychological vs. Pharmacological Treatment Studies

Concurrent psychotropic medication use is generally well controlled in comparative treatment studies with only one study having failed to prohibit concurrent psychotropics (Table 2.2. 15), although a post hoc analysis in this study failed to find any difference in treatment response between patients taking concurrent psychotropic medication and those who were not. Two other studies operated partial controls of similar dubiety to those mentioned previously by prohibiting the use of antidepressant medications but not other psychotropics (Table 2.2. 6,19). The remaining 17 studies all prohibited the use of concurrent psychotropic medication but did employ variable wash-out periods, from 7 days (Table 2.2. 9,10), to 28 days (Table 2.2. 13,20).

Again few studies (Table 2.2. 14) employed screens to identify surreptitious drug use.

Controls for concurrent psychological treatments in comparative studies are less impressive. Many studies simply do not mention concurrent psychological treatment (Table 2.2. 1-3,5,9,11,16-18). Others fail to control for concurrent psychological treatments as a result of basic study design. As was the case for psychological treatment studies, in these studies all treatment groups were given programmed practice self exposure instructions in addition to their prescribed research treatment. Some studies have required patients to be free from concurrent psychological treatments (Table 2.2. 10,13,14,19). These studies did not, however, specify any time limit on how recent any previous psychological treatment could be, prohibiting such treatments for the duration of the study only. As it is unlikely that psychological treatments can be said to "wash-out" within a predetermined and relatively short time span (e.g. 1 week), some reasonable time should have elapsed between the end of any psychological treatment and the start of study treatments. One study (Table 2.2. 20), included a "wash-out" time of 6 months between previous psychological treatments and study treatments. Although this may seem more satisfactory, it is nonetheless an arbitrary choice of timescale. If psychological treatments bring about lasting changes in patients, it is possible that they may not "wash-out" in any meaningful sense at all.

2.6.3 Design Solutions

An adequate study should be expected to control for concurrent drug and psychological treatments. For concurrent psychotropics the solution is a straightforward ban on the use of non study psychotropics with a pharmacologically sound wash-out period. For concurrent psychological treatments problems arise over how close to the study treatment such concurrent treatments can be allowed to occur. One solution might be to exclude any patient with any previous exposure to any psychological treatment. This would greatly reduce study recruitment rates. Such a strategy would mean that study populations were comprised mostly of cases of recent onset and short duration and thus would not be representative of the more chronic cases seen in wider clinical practice. Controls for concurrent treatments do have some cost. Any control that restricts concomitant treatments is likely to restrict

study access thus reducing recruitment rates and sample representativeness. The obvious exclusion of patients who are unable to discontinue concurrent psychotropic medications is a good example of this. The extent to which patients who are able to discontinue concurrent psychotropic medication differ from those who are not is not yet clear. Further research on the possible differences between patients who are able to discontinue concurrent treatments and those who are not, particularly with regard to treatment response, may help clarify this difficult area.

2.7 Assessment of Treatment Outcome

Assessment of treatment outcome in wider clinical practice is frequently unstandardised and limited in scope. Research assessment requires a broad range of standardised and comprehensive measures to adequately reflect process and outcome. This might at first appear to be an area where there is little dilemma in reconciling the conflicting demands of research and clinical practice, nevertheless there are some problems.

2.7.1 Psychological Treatment Studies

Many previous studies have employed inadequate assessment procedures, using only non-standardised measures (Table 2.1. 9,10,18,22,24), or focusing on only one aspect of the disorder, usually avoidance (e.g. Table 2.1. 1,2). It has been suggested (Kellner & Uhlenhuth 1991) that as there is no consensus on the boundaries of the constructs underlying anxiety and the anxiety disorders, the focus on specific factors such as avoidance may be premature. Surprisingly many studies have omitted to assess anxiety state in any way (Table 2.1. 1-4,6,8,11,14,33), with only 7 studies employing both therapist and patient rated measures of anxiety level (Table 2.1. 16,20,21,23,26, 28,34). The outcome measure common to most studies is percentage of patients panic free at treatment end point. Methods employed to assess panic attack frequency vary greatly between studies and the comparability of results is questionable. Percentage of patients panic free at end point may be an unreliable and overly optimistic measure of treatment outcome (Barlow 1988, Shear & Maser 1994). The assessment of panic attack frequency in most studies is made retrospectively thereby tending to overestimate the occurrence of panic (Rapee et al

1990b, De Beurs et al 1992). Prospective diary based methods are advocated as a more suitable alternative. Some studies record only panic attacks, specifically excluding limited symptom attacks (Table 2.1. 27,34). It is currently unknown whether this is a restrictive assessment procedure, although some data suggests that panic attacks may be regarded as equivalent to limited symptom attacks (Margraf et al 1987, Katerndahl 1990, Krystal et al 1991, De Beurs et al 1994). Further problems arise in some studies where patients were tutored as to the number of symptoms required for a definition of a panic attack (4 symptoms or more), (Table 2.1. 23,24,34), potentially influencing patients recording of panic attacks. The nature of this influence (increasing or decreasing reporting) remains unknown and requires further investigation. The majority of studies discuss and report panic attacks in terms of frequency or retrospective composite ratings of frequency and intensity. Possible panic attack variables such as prospectively rated intensity and duration of panic attacks are rarely employed and their status as outcome variables remains unclear.

A further point regarding assessment concerns the personnel who conduct the assessments. Whilst psychological therapists can provide important insights into change in treatment, they are not blind to treatment condition. Therapist bias or treatment allegiances, whether conscious or unconscious, may influence assessments. The use of independent assessors who are blind to treatment group is to be recommended. The majority of studies reviewed did not use an independent assessor, with most limiting assessments to patient rated measures only. The use of an independent assessor is an essential element of a sound methodology, but the strategy does have some drawbacks. The use of blind independent assessors throughout treatment would be a cumbersome procedure that may have a negative effect on compliance. A compromise solution is for therapists to conduct process assessments throughout treatment with end point assessments conducted by a blind independent assessor. This method has been employed in 6 studies (Table 2.1. 1,3,7,16,20,28). The use of an independent assessor at any point in treatment also requires checks to be made on inter-rater reliability.

2.7.2 Psychological vs. Pharmacological Treatment Studies

The situation described above for psychological treatment studies applies equally to the psychological vs. pharmacological treatment studies. Early studies in this area also failed to assess anxiety level and focused more on measures of avoidance (Table 2.2. 4,14). The measure common to most studies was again percentage of patients panic free at treatment end point, with there being the same problems with retrospective measurement of panic attacks, and exclusion of limited symptom attacks in these assessments (Table 2.2. 13,15). Other studies also tutored patients on the number of symptoms required for a classification of a panic attack (Table 2.2. 10,13) with the same ramifications for measurement. Again other possible panic attack variables such as severity or duration of attacks have not been investigated.

2.7.3 Design Solutions

The first problem in attempting to design an inclusive and comprehensive assessment package for use in panic disorder treatment outcome studies is the lack of agreement over what measures should be included in such a package (Kellner & Uhlenhuth 1991). Fortunately the recent deliberations of the Consensus Conference on Standardised Measurement for Panic Disorder Research have now been published (Shear & Maser 1994). The Conference suggested that treatment outcome should be measured across several domains and recommended that measures of anxiety, depression, anticipatory anxiety, fear of bodily sensations, and panic related fear and avoidance should form the basic core of any assessment package. The Conference also recommended that panic attacks and limited symptom attacks should be recorded by prospective diary based methods. The inclusion of separate ratings of panic and limited symptom attack intensity and duration would also be of interest. Further assessments were suggested for impairment of work, social and family life and also the use of global assessments of severity and outcome preferably completed by therapist, patient and if possible a third party such as an independent evaluator or referring clinician. The improvements to assessment procedures suggested by the Conference are likely to enhance the measurement of treatment outcome, although few studies have as yet adopted these procedures (Table 2.1. 28,34. Table 2.2. 20). A further problem is the size, complexity and time consuming nature of the required assessment procedure.This has led to suggestions (King 1997, Sharp et al 1997b)

that there may be some value in investigating measures that are more suitable to use in wider clinical practice, particularly in the primary care setting.

2.8 Analysis of Outcome

In wider clinical practice patients receive varying amounts of treatment and are regarded as having completed treatment at whichever point is appropriate to their individual circumstances. In explanatory research designs, there is a need to ensure equivalence between treatments and that all treatments are offered under optimal conditions. Thus for the purpose of explanatory design and subsequent analysis patients should all receive equivalent amounts of treatment. There is an obvious dilemma here in attempting to balance the demands of research and wider clinical practice, and considerable debate over appropriate study design and analysis plans.

2.8.1 Psychological Treatment Studies

All of the 36 psychological treatment studies reviewed carried out analyses on full completers samples where data were analysed only for those patients who completed the entire treatment period. This is not representative of wider clinical practice and may bias outcome in favour of the treatments under investigation as the results of treatment drop-outs cannot influence the analysis. This is especially the case for treatments with high drop-out rates. An intent to treat analysis which is more akin to wider clinical practice, may nonetheless bias against treatments by allowing early drop-outs an undue influence. None of the studies reviewed employed an intent to treat analysis. Thus in opting for a full completers analysis all of the studies reviewed employed the less stringent method of analysis which was more likely to bias outcome in favour of the treatments studied depending on the drop-out rates recorded for each treatment. Whilst drop-out rates are commonly recorded in the studies reviewed, their influence on outcome analyses is rarely discussed. A compromise solution to the problems inherent in both full completers and intent to treat analyses may be provided by a defined completers analysis which includes with full completers the results for patients who have completed treatment up to a pre-determined minimum, often half the full treatment period. Thus those with an unrealistically brief experience of treatment do not influence the results, nor is

analysis restricted solely to those who fully complete treatment. Somewhat surprisingly, none of the psychological treatment studies employed a defined completers method.

Further dilemmas can arise in that an outcome that achieves conventional levels of statistical significance may nonetheless be of little importance clinically. More stringent methods of assessing the clinical significance of outcomes are required. Several studies have employed methods of assessing clinical significance or high end-state functioning (Table 2.1. 8,12,14,15,20) which were unique to each study making comparisons between studies difficult. Standardised procedures for assessing clinical significance of outcomes based on explicit statistical criteria have already been established (Jacobson & Truax 1991). The procedures entail the calculation of cut-off scores on target measures and have been employed in several studies (Table 2.1. 16,21,26,27,34). These procedures have also been criticised for failing to take account of the magnitude of change (Hollon & Flick 1988), and for failing to relate criteria of clinically significant change to the social validity or relevance of that change (Baer 1988). The process of establishing a cut-off score on a given measure and assuming that scores below that cut-off reflect a clinically significant change will also be valid only to the extent that the chosen target measure accurately reflects the clinical condition being assessed. That is to say, the target measure must have sufficient construct validity. As previously mentioned there is still debate on the constructs representative of anxiety and the anxiety disorders (Kellner & Ulenhuth 1991). Early discussions on the issue of clinical significance (Kazdin 1977, Strupp & Hadley 1977) suggest that clinical significance might also be assessed by obtaining global ratings of change from patients, clinicians, or other significant observers. This method has the appealing directness of asking those undergoing a treatment to rate its effect upon them. Global ratings may also avoid the problems of construct validity of chosen measure, given that the constructs which global ratings reflect are by definition less specific, for example global severity or distress, or global change or improvement. Global scales are rarely used in treatment outcome studies and then usually for either patient or therapist (Table 2.1. 21,23,28), rather than for both.

Assessing treatment outcome at follow-up is important. This is recognised in the majority of studies (21 of 36) which include follow-up analyses. Unfortunately none of the studies took account of treatment received during the follow-up period. Thus

it cannot be clear whether results gained at follow-up can be attributed to the experimental treatments or to additional treatments given during the follow-up period. This is an important point with direct bearing on the value of follow-up results. Follow-up results contaminated by intervening treatment have little explanatory value. One study (Table 2.1. 26) did note intervening treatment but did not take account of this in the analysis of the follow-up data. Where it is difficult to ensure the absence of intervening treatment during the follow-up period, the occurrence of such treatment should be noted and these patients excluded from follow-up analysis.

2.8.2 Psychological vs. Pharmacological Treatment Studies

The same problems in analysis of outcome, as outlined above, occur for the psychological vs. pharmacological treatment comparative studies. The majority of these studies also employ full completers analyses with the attendant potential to bias outcome in favour of the treatments studied. One study (Table 2.2. 18) also employed an intent to treat analysis. The recommended compromise analysis, the defined completers analysis, was used in 4 of the 20 studies reviewed (Table 2.2. 3,14,15,20). Regarding the assessment of clinical significance of outcome, several comparative studies have employed methods of assessing clinical significance or high end-state functioning according to criteria unique to each study (Table 2.2. 3,10,11,14,15,18). Standardised procedures for the assessment of clinical significance (Jacobson & Truax 1991) were employed in only one study (Table 2.2. 20), and global measures of outcome in only two studies (Table 2.2. 13,14). The assessment of status at follow-up is surprisingly much less common in the comparative studies with only 5 studies including follow-up assessments. Of these 5, three did not assess whether any intervening treatment had occurred during the follow-up period and their results cannot therefor be relied upon. Only two studies carried out follow-ups on samples free from intervening treatment (Table 2.2. 14,20).

2.8.3 Design Solutions

Clinical relevance and comparability between studies could be enhanced by the use of a defined completers analysis. Such a method still involves some potential controversy with the selection of an acceptable minimum period of treatment for

defined completer status being essentially an arbitrary decision. The clinical significance of outcomes should be assessed preferably using available standardised methods. Follow-ups should be regarded as an important part of any treatment study and should include a record of, and a control for, intervening treatments. Little obvious cost would result from the adoption of these procedures, although these more stringent methods of assessment might depress current estimates of treatment efficacy especially at follow-up.

2.9 Miscellaneous

The foregoing discussion has covered the major dilemmas of treatment outcome research design and has suggested potential improvements to study design. Other points merit attention. As these apply equally well to psychological treatment studies and to psychological vs. pharmacological comparative treatment studies they will not be discussed separately for each study type.

Method of patient recruitment may be important, as it has been suggested (Aronson 1987b), that self-referred patients may differ in presenting characteristics from those referred by medical practitioners. An inspection of Table 2.1 and Table 2.2 highlights the variation in recruiting source of samples. Also the setting where the study is actually conducted may be important. Most studies have been conducted in specialist hospital or university clinics with patients travelling to these facilities to receive treatment, rather than being seen in their local primary care health centre. This is perhaps a surprising arrangement given that the majority of panic disorder and agoraphobia cases are seen and treated in the primary care setting (Ashcroft et al 1988, Katerndahl & Realini 1995). The applicability of the findings of previous research to patients treated in primary care has been questioned (Wilkinson & Lewis 1990). The effect of this study setting on sample configuration and treatment outcome has not been investigated empirically as yet.

Therapist competence is also an area that may require further attention. There is considerable variation across studies in the clinical experience of the personnel employed as therapists ranging from undergraduate students through postgraduate doctoral students to qualified clinical practitioners. This variation in experience may influence research findings. The clinical competence of therapists may also have a

bearing on treatment outcome. This is a sadly neglected topic although recent research has confirmed that therapist competence can influence outcome results in the area of anxiety disorders (Kingdon et al 1996).

2.10 Conclusion

In conclusion it is hoped that the points raised in this review might serve to stimulate further debate on study design and methodology, which is the foundation on which any scientific endeavour rests. The main issues highlighted in this review have been presented in detail by Sharp & Power (1997a) and Sharp & Power (Submitted)(a).

The review set out to be neither exhaustive nor conclusive, rather the aim was to highlight the dilemmas inherent in psychological and psychological vs. pharmacological treatment study design, and to outline methodologies which might overcome these problems. In virtually every case, however, the solutions to methodological inadequacies have an associated cost. In deciding whether research should, or should not, exert the extra effort necessary to conduct more rigorously controlled studies with hopefully more valid outcomes, the demands of wider clinical practice must continue to have relevance. Research must have clinical relevance. This final point is, after all, one of the main reasons why we conduct treatment outcome research.

CHAPTER 3. OUTLINE AND AIMS OF THE PRESENT RESEARCH

3.1 Introduction

Chapter 1 summarised panic disorder with or without agoraphobia as a prevalent, clinically demanding condition, which presents predominantly in the primary care setting. There is therefor considerable pressure to develop effective treatments for the condition, and to demonstrate their efficacy in a manner relevant to wider clinical practice. Evidence for the efficacy of pharmacological and psychological treatments has been provided by studies of medications and psychological treatments used singly or in combination. These studies have varied in design and quality and various attempts have been made to assess the relative merits of pharmacological and psychological treatments while controlling for this variation in methodology. Meta-analysis was described as a technique commonly used to overcome between study differences in methodology. Chapter 1 concluded, however, that within study control was more effective than the post hoc controls employed in between study analyses, and, consequently, a controlled comparison of a pharmacological and a psychological treatment was recommended. Recent interest has been shown in the selective serotonin reuptake inhibitor (SSRI) antidepressants and psychological treatments based on cognitive behaviour therapy, however, there are few comparisons of SSRI medications with cognitive behaviour therapy in recent meta analyses. More importantly, no previous study has adequately compared an SSRI medication with cognitive behaviour therapy and an adequate comparative trial of these two treatments is therefor timely and important. Such a comparison would have to recognise and address the methodological shortcomings of previous treatment outcome research. Chapter 2 critically reviewed previous treatment outcome study methodology, both in terms of scientific validity and applicability to wider clinical practice. This latter point was emphasised as an essential component of any valuable clinical study. The need to recognise and accommodate clinical reality in research design will be central to the studies conducted in the present research. In Chapter 2 various suggestions were made to improve on scientific control and ecological validity, and their cost in use discussed. These recommendations were considered in the design of the present study which represents a controlled investigation of the relative and combined efficacies of two treatments for panic disorder with or without agoraphobia conducted in the primary care setting. The treatments studied were the

SSRI, fluvoxamine and the psychological treatment, cognitive behaviour therapy. The overall aim of the investigation was the assessment of treatment efficacy with emphasis placed on the clinical relevance of findings. The study is reported as the Main Study (Chapter 4), followed by the Global Measures Study (Chapter 5), The Panic Attack Measures Study (Chapter 6), and finally the Prognostic Indicators Study (Chapter 7). A concluding discussion is presented in Chapter 8.

3.2 Main Study

Reported as Chapter 4. A controlled comparison of the relative and combined efficacies of the SSRI fluvoxamine and cognitive behaviour therapy in the treatment of panic disorder with or without agoraphobia. The comparison was undertaken within a 5 group framework and comprised a comparison of fluvoxamine, placebo, fluvoxamine plus cognitive behaviour therapy, placebo plus cognitive behaviour therapy, and cognitive behaviour therapy alone. This was the first time that this five group framework, essential to any comparison of a pharmacological and a psychological treatment, had been employed in an outcome study with panic disorder patients. The 5 group design is the minimum design standard required to permit the assessment of the relative and combined efficacies of the treatments under investigation. To ensure a meaningful comparison of the relative efficacies of the pharmacological and psychological treatments, therapist contact was balanced between groups. The use of concurrent treatments for panic disorder and agoraphobia, both pharmacological and psychological, was prohibited during the treatment phase of the study. Outcome was assessed across a range of therapist and patient report measures of general anxiety, agoraphobic avoidance, panic attacks, and depression. To enhance the clinical relevance of the results, the study was conducted in the primary care setting with all patients receiving treatment in their local surgery or health centre. The study design attempted to balance the requirement for scientific control to achieve meaningful results, with the need for methodology and procedure to match wider clinical practice as closely as possible, whilst at the same time taking account of the previous methodological problems highlighted in Chapter 2.

3.3 Global Measures Study

Reported as Chapter 5. An investigation of the relative and combined efficacies of fluvoxamine and cognitive behaviour therapy in the treatment of panic disorder with or without agoraphobia with treatment outcome expressed in terms of brief global measures more suited to use in wider clinical practice, particularly the primary care setting. Treatment outcome research of the type reported in Chapter 4 often employs cumbersome assessment procedures such as long self-report or therapist report scales which do not easily lend themselves to use in wider clinical practice, particularly the primary care setting where time is often limited and consultation times short. It is important therefor to demonstrate that improvement that is identifiable using these research-based assessment measures can also be picked up using more brief global measures suitable for use by the primary care clinician. This section of the study reports an investigation of the value of global ratings of outcome, and ratings of general wellbeing and social disruption, as treatment outcome measures. Ratings of outcome were completed by, psychologist therapist, general practitioner, and by patients themselves. If shown to be useful, these global measures would provide a viable, and more succinct, method of assessing outcome in wider clinical practice.

3.4 Panic Attack Measures Study

Reported as Chapter 6. Previous studies have tended to report outcome in terms of panic attacks as proportion of patients panic free at treatment end point only. This study attempted a more detailed investigation of panic attack and limited symptom attack variables as treatment outcome measures. The study was of an exploratory nature and included measures of panic and limited symptom attacks, such as rated intensity and duration of attack, in addition to the simple measures of frequency commonly employed in previous studies. Previous studies have often excluded limited symptom attacks from their analyses. It is not clear as yet whether such exclusion is warranted as few studies have compared panic with limited symptom attacks in a controlled fashion. Measures of panic attack and limited symptom attack frequency, severity, and duration were recorded pre, mid, and post treatment using a

prospective event recording method via patient diaries. These measures were employed within the controlled comparison of fluvoxamine, placebo and cognitive behaviour therapy in the treatment of panic disorder with or without agoraphobia reported as Chapter 4. The aim of the study was twofold, to assess the value of panic attack measures as treatment outcome indicators, and to assess their ability to discriminate between differing treatments in a controlled comparison in patients with panic disorder and agoraphobia. A within subjects comparison of panic attacks vs. limited symptom attacks at each assessment point was also undertaken.

3.5 Prognostic Indicators Study

Reported as Chapter 7. The previous chapters in the present study have reported on treatment outcome in terms of research based measures, global clinically appropriate measures, and panic attack based measures. Whilst measuring outcome is of course important, it has long been an ambition of clinicians to attempt to predict treatment response preferably from pre-treatment measures. Such ability holds the promise of more precise programmes of pre-treatment screening and treatment allocation. Previous attempts at predicting treatment outcome from pre-treatment assessments have employed either inadequate between group designs, or have used multiple regression strategies. Whilst the latter do illustrate the amount of variance in treatment response accounted for by pre-treatment measures, they do not give any indication of the clinical significance of the predictions they provide. There is little practical value in a perfect prediction of a clinically meaningless outcome. Other methods of assessing prognostic indicators are therefor required. The aim of the reported study was an investigation of measures of mood state, personality and social disruption as pre-treatment prognostic indicators of treatment response in the patients receiving pharmacological (fluvoxamine), or psychological (cognitive behaviour therapy), treatments for panic disorder with or without agoraphobia as part of the main study reported as Chapter 4. The study design employed a logistic regression analysis for the first time with patients with panic disorder and agoraphobia, and is therefor of an exploratory nature.

CHAPTER 4 MAIN STUDY

4.1 Introduction

This study is an attempt to address the methodological shortcomings of previous comparative studies of psychological and pharmacological treatments for panic disorder and agoraphobia outlined in Chapter 2. Many studies have investigated the relative and/or combined efficacies of psychological and pharmacological treatments for panic disorder and agoraphobia. Unfortunately, this research suffers from a series of methodological flaws that compromise outcome findings. Firstly, as discussed in Chapter 2, many studies neglect to control for concurrent treatments, both pharmacological and psychological, received along with the study treatment. The presence of such concurrent treatment makes interpretation of study results extremely difficult. Secondly, no study comparing a psychological treatment with a pharmacological treatment for panic disorder within a placebo controlled framework has employed a psychological treatment alone group, with all previous studies using a psychological treatment plus placebo treatment to represent this group. It was suggested in Chapter 2 (c.f. Hollon & DeRubies 1981), that a complete study comparing a drug with a psychological treatment must employ five treatment groups, namely, drug, placebo, drug plus psychological treatment, placebo plus psychological treatment, and psychological treatment alone. A third problem for comparative studies has been the lack of control for therapist contact. When comparing a relatively time-consuming treatment (cognitive behaviour therapy) with a comparatively quickly administered treatment (medication), it is essential to attempt to balance treatments for therapist contact time to try to control for this possible confounding factor. The fourth problem with previous research studies discussed in Chapter 2, is the variation between studies in quality and quantity of outcome assessment. Finally, whilst it is recognised that the bulk of morbidity in the anxiety disorders is encountered in general practice (Ashcroft et al 1987), previous treatment outcome studies on panic disorder and agoraphobia have been conducted in specialist clinics or hospital settings. This has led some (Wilkinson & Lewis 1990) to question the applicability of this previous work to the majority of patients who do not reach specialist hospital settings.

The present study attempts to correct these methodological problems by (a) requiring that all patients received no concurrent psychological treatments for 6 months prior to study entry, and no concurrent psychotropic medication during the treatment phase of the study. Patients referred to the study whilst taking concurrent psychotropic medication were required to undergo a 28 day wash-out period prior to study entry; (b) employing a

five group methodology, including a psychological treatment alone group; (c) ensuring that an attempt is made to balance therapist contact time across all groups; (d) assessing treatment outcome across a range of patient and therapist rated measures of anxiety, depression and avoidance, including prospective monitoring of panic attacks, with treatment end-point assessments conducted, where possible, by an independent assessor blind to treatment group; and (e) conducting the investigation in the primary care setting. The study involves randomised allocation to treatment group and is conducted double-blind for medication. This study is also the first to compare the relative and combined efficacies of cognitive behaviour therapy and the SSRI fluvoxamine within a controlled 5 group framework, and entails a comparison of fluvoxamine (FL), placebo (PL), fluvoxamine plus cognitive behaviour therapy (FL+CBT), placebo plus cognitive behaviour therapy (PL+CBT), and cognitive behaviour therapy (CBT).

4.2 Method

4.2.1 Subjects

Patients were recruited via referral from general practitioners (GP) and were those considered suitable for pharmacological and/or psychological treatment. All patients were seen for all appointments in their local GP clinic. Following initial GP assessment and referral, patients were seen by a Clinical Psychologist for semi-structured interview to ascertain patient characteristics, presenting condition and severity of illness. The following entry criteria were employed.

4.2.2 Inclusion/Exclusion Criteria

4.2.2.1 Inclusion Criteria

(a) Patients presented with panic disorder with or without agoraphobia which conformed to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition - Revised criteria (DSM III-R, APA 1987); (b) Patients scored a minimum of 15 on the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959) at both entry (Day -7) and after one week wash-in (Day 0); (c) Duration of the problem greater than or equal to 3 months; (d) patients aged between 18 and 70 years inclusive; (e) patient willing and able to provide informed written consent to participation.

4.2.2.2 Exclusion Criteria

(a) Patients on any concurrent psychotropic medication, all patients were required to undergo a 4 week wash-out from concurrent psychotropic medication prior to entry, if required; (b) Patients suffering from a major depressive disorder as operationalised as a score of 21 or greater on the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979); (c) patients suffering from obsessive-compulsive disorder, paranoid personality disorder, schizophrenia, schizo-affective disorder, manic disorder, or other unspecified psychosis; (d) patients with severe concurrent somatic disease, particularly impairment of hepatic/renal function, or heart disease of significant clinical importance; (e) patients with evidence of epilepsy, organic brain disease, or other serious neurological deficit; (f) patients who were alcohol dependent or drug dependent, or showed a risk of dependency; (g) patients considered a high suicide risk; (h) female patients who were pregnant, breast feeding, or who were not taking adequate contraceptive precautions; (i) patients who suffered from a physical disability which severely restricted mobility; (j) patients who had received psychological treatment for panic disorder and agoraphobia within the 6 months prior to entry; (k) patients who attended other therapists whether lay or professional.

Over a period of 3 years a total of 238 patients were referred by GPs for study inclusion. Of these, 45 were not entered for the following reasons: - 8 patients failed to attend for assessment, 5 declined entry at first appointment, 14 were classified as disorders other than panic disorder and agoraphobia, 5 failed to meet the criteria of the DSM III-R classification, 5 scored less than 15 on the HAM-A, 5 declined to discontinue concurrent psychotropic medication for the prescribed wash-out period, 2 were assessed as a serious suicide risk, and 1 patient was suffering from concurrent illness (epilepsy). A total of 193 patients were, therefore, entered into the study.

4.2.3 Procedure

At Day -7 patients were randomised to CBT alone or to the medication groups. Those patients in the medication groups received 1 week of single blind placebo medication at one tablet placebo/day, (Day -7 to Day 0). This procedure was employed to control for the effect of early placebo responders on outcome in the medication groups. All patients scoring below the established minimum of 15 on the Hamilton Anxiety Scale (HAM-A) at Day 0 were to be excluded. No exclusions on this criterion

were made. Three patients were excluded from the trial during the placebo wash-in week, one patient used psychotropic medication, one patient refused further participation, and one patient did not return for further treatment. At Day 0 all patients in the medication groups who continued to satisfy entry criteria were randomised to one of the 4 groups receiving medication, i.e. FL, PL, FL+CBT or PL+CBT. Patients in the CBT alone group did not receive the single blind placebo during wash-in. No patients in the CBT group were excluded during this period (Day -7 to Day 0). A total of 190 patients were, therefore, entered into the randomised phase of the study at Day 0. All patients were thereafter seen for the same number of sessions to the same schedule of contact. Each session lasted a maximum of 60 minutes and a minimum of 30 minutes. All patients were seen by the one clinical psychologist therapist. A random sample of appointments were audio taped as a check on treatment integrity. Patients were then seen at Day -7 and 0 for initial assessment. Following Day -7 and Day 0 appointments, all patients were seen for assessment and treatment at Day 7, Day 14, Day 28, Day 42, Day 56, Day 70 and at Day 84 when end point assessment was carried out. Follow up at 6 months was also carried out. At each session all patients were asked to report any medication taken since the last visit. Patients were notified at entry that the use of non-study psychotropic medication would result in withdrawal from the study. Patients continued to have access to their GP.

Access to the study investigators outside of treatment sessions was available via telephone or radio pager. Patients who failed to complete the entire study period having withdrawn due to early effectiveness or ineffectiveness, who received at least 42 days treatment, and who provided adequate end-point data were included in the final analysis as "defined completers". A total of 149 completers and defined completers from the entry group of 190 were included in the final analysis. Details of completers, defined completers and the drop out/withdrawals per group are given in Table 4.1, demographic details for each treatment group included in the analysis are given in Table 4.2.

4.2.4 Treatments

4.2.4.1 Medication

Following 1 week of single blind placebo, patients in the FL and PL groups received 12 weeks of either fluvoxamine or placebo. Patients receiving fluvoxamine received an initial dose of 50mg/day fluvoxamine at Day 0, this was increased by 50mg to 100mg/day at Day 7, and by a further 50mg to 150mg/day at Day 14. Thereafter the dose was

maintained at 150mg/day for the remaining 10 weeks of the study period. Medication was discontinued without taper at Day 84. Medication was supplied in 50mg tablets, patients receiving placebo were given the equivalent number of tablets at each appointment thus maintaining the double blind status.

Table 4.1 Sample characteristics by group for number of patients randomised, completers, defined completers, patients excluded from analysis, drop-out, number included in completers analysis and proportion of completers sample with independent end point assessment.

	FL	PL	FL+CBT	PL+CBT	CBT
No randomised	36	37	38	36	43
Excluded/ drop-outs	7	9	9	3	13
Completers	24	20	27	32	30
Defined completers	5	8	2	1	0
No included in completers analysis	29	28	29	33	30
No (%) of patients in completers analysis with independent end point assessment	19 (65.5)	16 (57.1)	15 (51.7)	26 (78.8)	22 (73.3)

Table 4.2 Demographic features of (n = 149) completers sample

	FL (n = 29)	PL (n = 28)	FL+CBT (n = 29)	PL+CBT (n = 33)	CBT (n = 30)
Mean age (yrs)	36.62	42.28	37.27	38.81	33.23
Sex	M5, F23	M6, F22	M7, F21	M6, F27	M8, F22
Mean duration of panic disorder (Years since first panic attack)	7.32	7.74	7.00	6.93	5.11
Mean duration of agoraphobic avoidance (years)	5.04	3.75	6.18	8.35	4.04
Mean duration of current episode (months)	34.03	51.53	61.41	57.42	28.66

Patients who were unable to tolerate the maximum dose of medication had the dosage reduced from three to two tablets/day (i.e. 150mg/day to 100mg/day for the fluvoxamine

groups). Reduction was necessary for 8 patients, (FL = 2 patients, PL+CBT = 2 patients, FL+CBT = 4 patients). Compliance was assessed by return pill counts, no formal recordings of drug plasma levels were taken. Session content for the FL and PL groups focused on assessment of current status and progress. Patients were aware that the psychologist/assessor would not offer any therapeutic advice, and no direct advice on anxiety management was given. For example, patients who asked about anxiety or avoidance management were told, "you must feel free to do whatever you want to do". The emphasis in these groups was on the provision of a warm and empathic therapeutic relationship without the provision of active therapeutic advice. This was similar to the approach used by Power and colleagues (Power et al 1990a) in their study employing a 5 group, balanced therapist contact methodology.

4.2.4.2 Cognitive Behaviour Therapy

A cognitive behaviour therapy was employed which emphasised both gross exposure techniques and cognitive and behavioural panic management techniques as contributing factors to emotional processing (Foa & Kozak 1986) and thus fear reduction. The areas targeted in treatment were those outlined by Barlow and co-workers (Barlow 1988, Zinbarg et al 1992) and included (a) the action tendencies associated with panic, (b) the sense of lack of control, and (c) hypervigilant and avoidant information processing strategies. The first 2 sessions of treatment (Day -7 and Day 0) were given over to assessment. Patients detailed both gross avoidances, e.g. of situations, and more subtle control and avoidance behaviours employed in an attempt to control panic attacks, such as holding on to supports, or cognitive and behavioural distraction techniques. Patient's personal understanding of their panic attacks including any fears of catastrophic outcome were also investigated. At Day 0 patients were informed of the basic nature of panic attacks and informed that full explanation of their disorder would be given at their next appointment (Day 7). This educational component of treatment has previously been emphasised as important, (Shear & Francis 1988). Patients were informed that their spouse, partner or other relative could attend this appointment if desired. At Day 7 a full explanation of the likely causes, course and nature of patient's panic disorder was given. Treatment instructions were given in keeping with the above-suggested essential targets of change. Treatment emphasised the importance of patients confronting their panic attacks and attempting to replace avoidance responses, both behavioural and cognitive,

with more approach centred actions. In this way patients were enabled to appreciate that their worst fears were not realised and that if unsupported by avoidant actions their panic attacks dissipated and gradually settled over time. Treatment, therefore, attempted to follow the principles of emotional processing (Foa & Kozak 1986). Traditional exposure requiring a return to avoided situations was presented as a useful and ecologically valid means to encounter the panic attacks and thus present a forum for change. Artificial methods of panic provocation or simulation such as interoceptive exposure (Barlow 1988) were not employed. All patients received a standardised treatment manual (Appendix I) at the Day 7 appointment. All further sessions (Days 14-84) were devoted to a review of progress, discussion of any possible problems in treatment, and identification of future targets for exposure and change. Treatment was presented as a profoundly patient led endeavour with efforts between sessions seen as an essential component of change. This being the case, targets were decided by patients with therapist dictated "homework" being kept to a minimum wherever possible. Patients in the cognitive behaviour therapy group (CBT) received no medication throughout treatment.

4.2.4.3 Combined Treatments

Patients receiving either fluvoxamine + cognitive behaviour therapy (FL+CBT) or placebo + cognitive behaviour therapy (PL+CBT) received medication to the identical protocol and cognitive behaviour therapy to the identical protocol to those detailed above. The medication was emphasised as adjunctive or complementary to the cognitive behaviour therapy in the combined treatment groups in an attempt to engage an equal commitment to the cognitive behaviour therapy in these groups.

4.2.4.4 Therapists

All patients were treated by the current author, DS, a clinical psychologist with 13 years post qualification experience. A second clinical psychologist (KGP) with 16 years post qualification experience was the independent end-point assessor and provided cover for absences of the first author. A GP principal and consultant psychiatrist (RJS) acted as medical supervisor and carried the radio pager with occasional cover being provided by KGP and DS. Data collected were monitored by an independent monitor (JAA) at monthly intervals throughout the duration of the study.

4.3 Measures

Although a variety of treatment process and outcome measures were employed, only the main measures are reported here. Copies of all measures are given in Appendix II.

4.3.1 Mood

Anxiety was measured by the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959). This therapist rated scale was completed using a more structured scoring system than that originally used by Hamilton (1959) based on the frequency, severity and duration of symptoms (Hamilton Anxiety Glossary; Power et al 1983, Appendix III). The HAM-A was completed for all groups at Days -7, 0, 7, 14, 28, 42, 56, 70, 84 and 6 month follow up.

Patients provided a self rating of anxiety using the Kellner and Sheffield Symptom Rating Test (SRT) (Kellner & Sheffield 1973). This scale, designed as a measure of symptom change in neurotic patients undergoing treatment in therapeutic trials such as drug trials, was completed at Days 0, 7, 14, 28, 42, 56, 70, 84 and 6 month follow up.

Depression was rated by therapist rating using the Montgomery-Asberg Depression Rating Scale (MADRS), a scale designed to be sensitive to change in depression during treatment (Montgomery & Asberg 1979). This was completed at Days -7, 0, 42, 84 and 6 month follow up.

4.3.2 Phobic Avoidance

Avoidance was measured by means of the Fear Questionnaire (FQ) (Marks & Mathews 1979). This self rated instrument provides a rating of agoraphobic, social and blood injury avoidance and further ratings of mood disruption and global distress. For the sake of brevity only results from the Agoraphobia Subscale (FQ-AG) are reported here. This was completed at Days 0, 42, 84 and 6 month follow up.

4.3.3 Panic Attacks

Panic attacks were assessed by inspection of patients panic diaries which were completed for 7 day periods throughout the treatment phase of the trial. Patients were provided with the DSMIII-R list of panic symptoms and asked to identify those which had occurred during any one panic attack, and to provide an overall rating of intensity and estimate of duration for each panic attack. Patients were instructed that panic attacks

constituted episodes of anxiety of sudden onset but were not informed as to the number of symptoms required to constitute a panic attack in DSMIII-R. Panic attacks versus limited symptom attacks were thus assessed post hoc by the therapist. In this report for the sake of brevity, only the percentage of patients panic free at end point will be reported. More detailed analysis of panic data will be reported in Chapter 6.

4.4 Results

Table 4.1 lists the sample configurations for each group. The groups showed some difference in attrition with the PL+CBT group showing the lowest drop out/exclusion rate and the CBT group the highest. Drop out/exclusion rates were not statistically different across groups however ($x^2 = 5.99$, df = 4, n.s.). The proportion of defined completers differed significantly between groups ($x^2 = 16.604$, df = 4, $p < 0.05$) with the PL group having the highest number of defined completers (n = 8). The reasons for drop out or exclusion from completers sample were as follows: 1 patient from the FL group, 2 from PL, 3 from FL+CBT, 2 from PL+CBT, and 8 from CBT did not return for treatment. One patient from the FL group, 1 from PL, 1 from PL+CBT and 3 from CBT were found during treatment to have failed to meet study entry criteria, either by the emergence of a contra-indicated condition (e.g. alcohol abuse) or the use of concurrent psychotropic medication, these patients were excluded from analysis. One patient from the FL group and 1 from the CBT group stated ineffectiveness as the reason for drop out. One patient in the CBT group refused treatment after 3 sessions. Concern over study medication compliance or obvious failure to comply with medication regimen led to, 1 patient in the FL group and 3 patients in the PL group being excluded from analysis. One patient each from the PL and the FL+CBT groups were excluded due to administrative errors, namely failure to complete questionnaire assessments adequately. Drop out rates stated to be due to medication side effects were n = 3 (8.3%) for the FL group, n = 2 (5.4%) for the PL group, n = 0 for the PL + CBT group and n = 5 (13.1%) for the FL+CBT group. This gives a combined drop out rate attributed to side effects of n = 8 (10.8%) for those patients receiving Fluvoxamine.

A previous study (Power et al 1990a) had established a strong concordance (Pearson r = 0.86) on ratings made on the HAM-A by the personnel in the present study (KGP, DS). As a further check, correlations between Day 70 HAM-A scores and Day 84 HAM-A scores for all patients receiving independent end-point assessment were calculated, for

the whole sample and for each treatment group individually. Correlations obtained were, Whole Sample r = 0.82, FL r = 0.77, PL r = 0.87, FL+CBT r = 0.61, PL+CBT r = 0.90, CBT r = 0.85.

4.4.1 Statistical Analysis

One-way analysis of variance between groups on age, duration of panics and agoraphobic avoidance, duration of current episode, Day -7 and Day 0 HAM-A, Day 0 SRT, Day -7 and Day 0 MADRS, and Day 0 FQ+AG, revealed no significant differences. Groups were therefore comparable on the main dependant measures prior to active treatment and following one-week wash-in.

A one way analysis of variance between groups on total amount of therapist contact revealed a significant difference between groups ($F(4,144) = 16.86$, $p < 0.001$). Using post hoc Scheffe tests, FL ($x = 360.38$ min, s.d. = 27.42) differed from FL+CBT ($x = 395.17$ min, s.d = 45.85) ($p < 0.05$); whilst both FL and PL ($x = 380.07$ min, s.d = 39.77) differed from both PL+CBT ($x = 424.36$, s.d = 29.93) and CBT ($x = 422.66$ min, s.d = 38.92) ($p < 0.01$). This suggested that the procedural attempt to balance therapist contact time across groups had not been entirely successful. In order to assess the relevance of this difference in contact time as potential covariate in analysis, a specimen analysis was conducted. A change score was computed for all subjects by subtracting end point, Day 84, HAM-A scores from entry Day -7, HAM-A scores. A specimen analysis of covariance was conducted between groups on this score with total amount of therapist contact as the covariate. This yielded a non-significant covariate term ($F(1,143) = 2.19$, n.s.) suggesting that the covariate, total amount of therapist contact, had exerted little influence on treatment response as measured by HAM-A difference score. Inspection of scatterplots for total amount of therapist contact by HAM-A difference score for each group revealed an absence of obvious non-linear relationship between the variables. A final check comparing the observed and adjusted group means on HAM-A difference score for each treatment group revealed minimal differences again suggesting little influence of the covariate, total amount of therapist contact, on the dependant measure, HAM-A difference score. The observed versus adjusted means for each group were as follows, F (13.31 vs. 13.21), PL (7.50 vs. 7.45), FL + CBT (16.58 vs. 16.58), PL + CBT (15.51 vs. 15.58), CBT (14.90 vs. 14.96).

It appeared, therefore, that whilst there were some differences between the groups on total amount of therapist contact, these differences were not exerting a sufficient influence on outcome results to warrant the use of a full scale analysis of covariance. Also the assumptions of equal and linear regression within groups between the covariate and dependant variables, and the assumption that the covariate was not affected by the experimental (i.e. treatment group) variable required by an analysis of covariance (Huitema 1980) were not met by the data from this study. A full scale analysis of covariance was, therefore, liable to yield results of dubious validity and was thus deemed inappropriate.

Main treatment effects were, therefore, investigated using repeated measures analysis of variance (ANOVA) with treatment group as the between subjects factor and time of assessment as the within groups factor. F-tests for simple effects were then carried out for each time of assessment, and specific between group differences illustrated using post-hoc Scheffe tests. The Scheffe test was chosen as a conservative criterion minimising the risk of type I error. Within group changes in scores were investigated by comparison of entry versus end-point scores using related t-tests.

4.4.2 Hamilton Anxiety Scale (HAM-A)

Table 4.3 lists the mean scores for the HAM-A for each group at each assessment point.

Two factor analysis of variance (treatment group and time of assessment) on HAM-A scores over the wash-in phase (Day -7 to Day 0) revealed a significant effect for time ($F(1,144) = 71.74$, $p < 0.001$) and an interaction effect ($F(4,144) = 4.15$, $p < 0.005$) indicating a differential reduction in HAM-A over wash-in between groups. Simple effects F-tests revealed a significant reduction in HAM-A score over wash-in for FL ($F(1,28) = 30.13$, $p < 0.001$), PL ($F(1,27) = 14.72$, $p < 0.001$), FL+CBT ($F(1,28) = 18.85$, $p < 0.001$) and PL+CBT ($F(1,32) = 31.31$, $p < 0.001$) but not for CBT ($F(1,29) = 0.10$, n.s).

Between groups analysis gave a significant group ($F(4,144) = 4.56$, $p < 0.002$) time ($F(8,1152) = 270.39$, $p < 0.001$) and interaction effect ($F(32,1152) = 4.89$, $p < 0.001$) indicating differential changes across groups.

Table 4.3 Means and standard deviations (s.d.) for Hamilton Anxiety Scale HAM-A for all groups at each assessment point during treatment.

HAM-A	FL	PL	FL+CBT	PL+CBT	CBT
DAY -7	21.3	21.4	21.4	22.0	19.8
	(3.7)	(4.5)	(3.6)	(4.2)	(3.6)
DAY 0	18.9	19.6	18.9	19.5	19.6
	(3.8)	(4.1)	(3.1)	(4.2)	(4.2)
DAY 7	16.8	17.9	18.2	16.5	17.1
	(5.6)	(5.3)	(5.6)	(5.3)	(5.5)
DAY 14	13.9	15.9	12.8	14.5	12.7
	(7.0)	(6.1)	(5.2)	(6.0)	(5.8)
DAY 28	11.6	16.0	9.6	12.1	11.3
	(6.9)	(6.1)	(5.6)	(5.8)	(5.8)
DAY 42	9.8	15.1	8.2	10.0	9.9
	(6.0)	(7.3)	(5.4)	(6.9)	(6.0)
DAY 56	8.5	15.0	6.5	9.0	8.1
	(5.9)	(7.7)	(4.9)	(6.5)	(4.4)
DAY 70	7.6	13	5.4	7.8	7.5
	(6.6)	(8.3)	(5.0)	(6.6)	(5.3)
DAY 84	7.9	13.9	4.8	6.5	4.9
	(7.0)	(8.4)	(5.7)	(6.7)	(4.4)

The data in Table 4.3. are further illustrated in Figure 4.1. overleaf.

FIGURE 1: MEAN HAM-A SCORES
FOR EACH TREATMENT GROUP
AT EACH STAGE OF ASSESSMENT

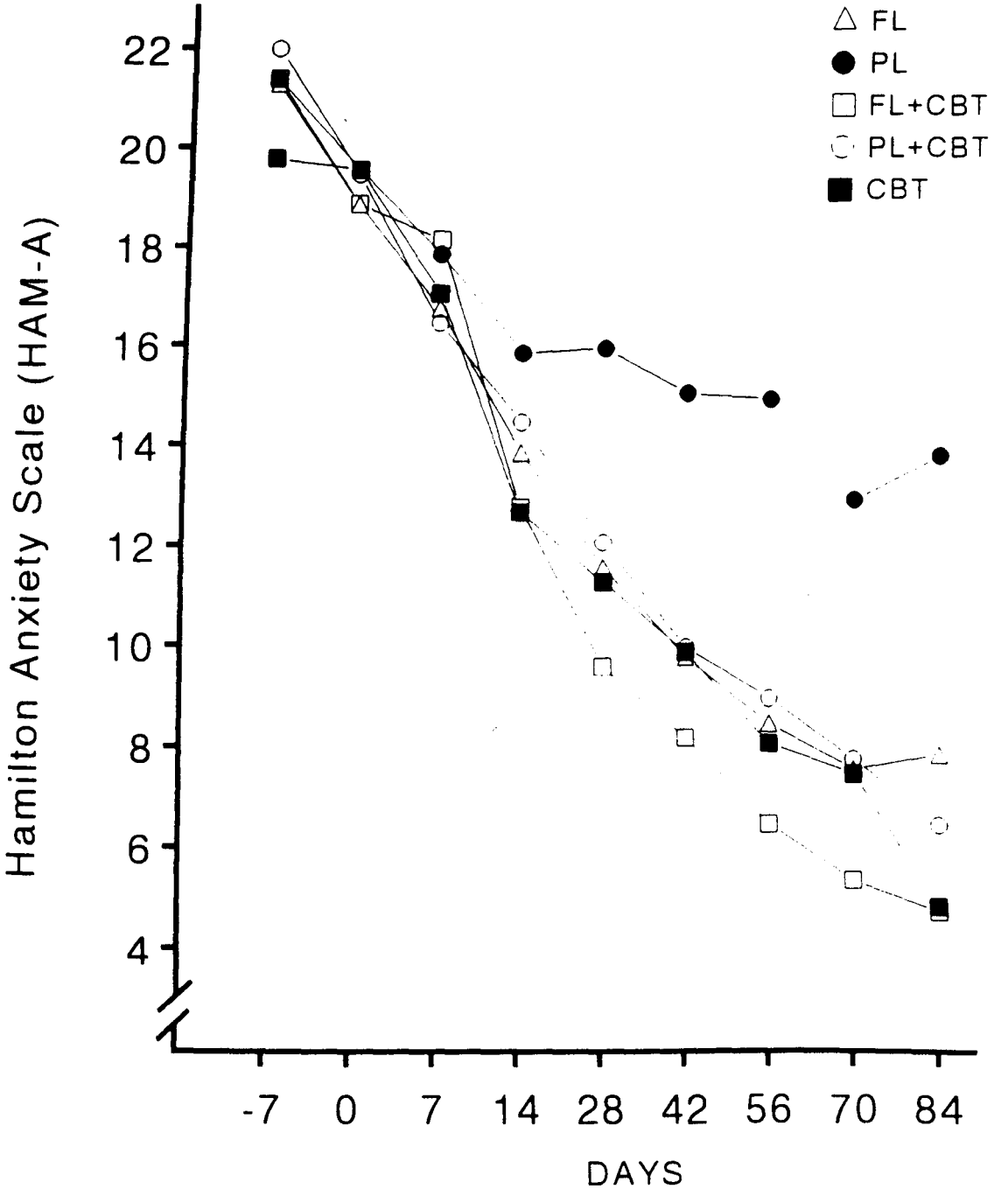

Table 4.4 Analysis of variance and simple effects on Hamilton Anxiety Scale (HAM-A) scores at each assessment point for all groups

(i)

Two factor ANOVA with repeated measures on B	**df**	**F**	**p**
Factor A (treatment group)	4, 144	4.56	0.002**
Factor B (time of measurement)	8, 1152	270.39	0.000***
Interaction A x B	32, 1152	4.98	0.000***

(ii) **Simple effects (SS, Factor A)**

	df	**F**	**p**	**Scheffe**			
Day -7	4, 144	1.30	0.272				
Day 0	4, 144	0.27	0.896				
Day 7	4, 144	0.55	0.697				
Day 14	4, 144	1.37	0.244				
Day 28	4, 144	4.34	0.002**	2-3**			
Day 42	4, 144	4.89	0.001**	2-3**	2-1*	2-5*	2-4*
Day 56	4, 144	8.39	0.0000***	2-3***	2-1**	2-5**	2-4**
Day 70	4, 144	5.49	0.0004***	2-3***	2-1**	2-5*	2-4*
Day 84	4, 144	9.29	0.0000***	2-3***	2-1*	2-5***	2-4**

(iii) **Simple effects (SS Factor B)**

	df	**F**	**p**
FL	8, 224	63.38	0.000***
PL	8, 216	11.08	0.000***
FL+CBT	8, 224	99.07	0.000***
PL+CBT	8, 256	76.42	0.000***
CBT	8, 232	68.32	0.000***

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

KEY : Post hoc Scheffe treatment group comparisons :

1 = FL, 2 = PL, 3 = FL+CBT, 4 = PL+CBT, 5 = CBT.

Groups separated by a hyphen differ significantly from each other.

From Table 4.4 it can be seen that no significant between group differences emerged until day 28 when the PL and FL+CBT groups differed. This difference persisted and widened throughout the treatment period. By Day 42 all other treatment groups (FL, FL+CBT

and CBT) differed significantly from PL with these differences being maintained at varying levels of significance throughout the treatment period. At no point did the active treatment groups show a statistically significant difference between them.

Within groups analysis revealed a significant reduction in HAM-A scores for all groups. Comparison of pre- (Day 0) and post- (Day 84) treatment HAM-A scores revealed a significant reduction for FL ($t = 10.993$, $df = 28$, $p < 0.0001$), PL ($t = 4.09$, $df = 27$, $p < 0.001$), FL+CBT ($t = 15.28$, $df = 28$, $p < 0.0001$), PL+CBT ($t = 14.45$, $df = 32$, $p < 0.0001$) and CBT ($t = 13.88$, $df = 29$, $p < 0.0001$).

4.4.3 Symptom Rating Test (SRT)

Table 4.5 lists the mean scores for the SRT for each group at each assessment point. These data are also illustrated as Figure 4.2.

Between group analysis gives a significant group ($F(4,144) = 3.96$, $p < 0.005$), time ($F(7,1008) = 65.63$, $p < 0.001$) and interaction effect ($F(28,1008) = 2.34$, $p < 0.001$) indicating differential changes across groups.

Table 4.5 Means and standard deviations (s.d.) on Kellner and Sheffield (SRT) for all groups at each assessment point during treatment.

SRT	FL	PL	FL+CBT	PL+CBT	CBT
DAY 0	33.5	38.4	33.0	33.9	35.5
	(17.2)	(18.2)	(15.5)	(14.3)	(16.6)
DAY 7	28.5	30.1	27.8	26.2	30.2
	(16.7)	(16.8)	(16.5)	(16.9)	(17.3)
DAY 14	24.0	30.7	18.9	23.4	23.1
	(16.6)	(18.0)	(14.0)	(16.4)	(15.5)
DAY 28	21.6	32.0	15.2	21.2	20.3
	(17.4)	(19.3)	(15.3)	(16.9)	(12.4)
DAY 42	20.2	31.4	13.9	17.5	19.9
	(17.7)	(21.1)	(15.3)	(16.4)	(14.2)
DAY 56	15.4	31.2	11.0	14.5	16.5
	(15.1)	(21.9)	(15.2)	(14.5)	(11.8)
DAY 70	14.4	27.2	9.2	15.3	16.7
	(17.3)	(22.1)	(14.7)	(17.3)	(14.6)
DAY 84	16.2	30.2	10.3	13.3	13.9
	(17.1)	(23.1)	(16.3)	(15.2)	(12.5)

FIGURE 2: MEAN SRT SCORES
FOR EACH TREATMENT GROUP
AT EACH STAGE OF ASSESSMENT

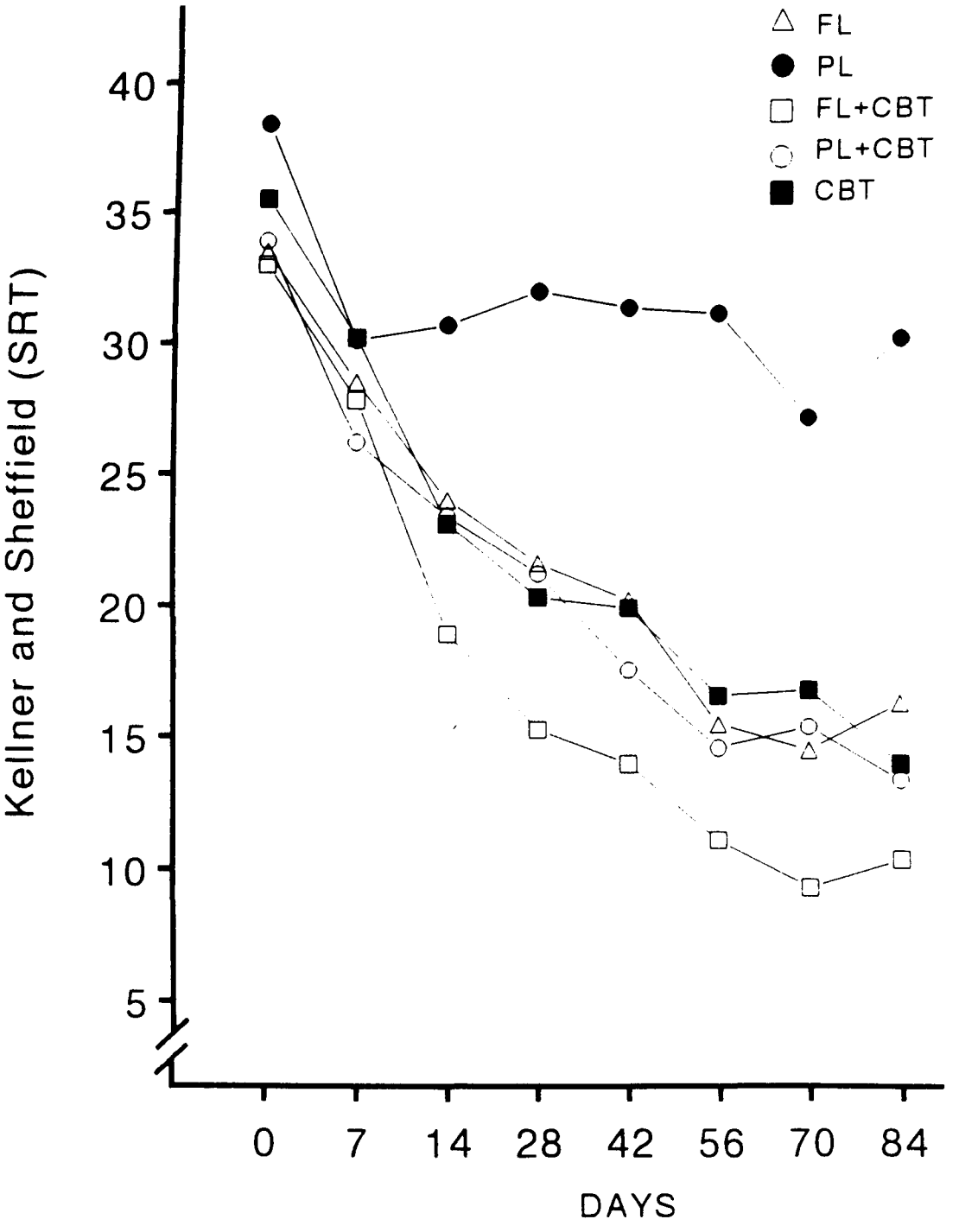

Table 4.6 Analysis of variance and simple effects on Kellner and Sheffield (SRT) scores at each assessment point for all groups

(i)

Two factor ANOVA with repeated measures on B	**df**	**F**	**p**
Factor A (treatment group)	4, 144	3.96	0.004**
Factor B (time of assessment)	7, 1008	65.63	0.000***
Interaction A x B	28, 1008	2.34	0.000***

(ii) **Simple effects (SS, Factor A)**

	df	**F**	**p**	**Scheffe**			
Day 0	4, 144	0.50	0.730				
Day 7	4, 144	0.31	0.869				
Day 14	4, 144	1.98	0.100				
Day 28	4, 144	3.97	0.004**	2-3**			
Day 42	4, 144	4.23	0.002**	2-3**	2-4*		
Day 56	4, 144	6.83	0.000***	2-3***	2-4**	2-5*	2-1*
Day 70	4, 144	4.08	0.003**	2-3***			
Day 84	4, 144	5.93	0.0002***	2-3**	2-4**	2-5*	

(iii) **Simple effects (SS, Factor B)**

	df	**F**	**p**
FL	7, 196	13.67	0.000***
PL	7, 189	2.41	0.02*
FL+CBT	7, 196	37.33	0.000***
PL+CBT	7, 224	17.60	0.000***
CBT	7, 203	16.37	0.000***

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

KEY: Post hoc Scheffe treatment group comparisons :

1 = FL, 2 = PL, 3 = FL+CBT, 4 = PL+CBT, 5 = CBT.

Groups separated by a hyphen differ significantly from each other.

Table 4.6 indicates that no significant group differences occurred until Day 28 when the PL and FL+CBT groups differed. This difference being maintained throughout the treatment period. The PL and PL+CBT groups differed significant on three occasions, Days 42, 56 and 84; the PL and CBT groups differed significantly on two occasions at Day 42 and 84 and the PL and FL groups differed significantly on one occasion at Day 56. There were no other between group differences. Comparison of pre- (Day 0) with

post- (Day 84) treatment scores for SRT within groups revealed a significant reduction for FL ($t = 4.96$, $df = 28$, $p < 0.001$), PL ($t = 2.61$, $df = 27$, $p < 0.01$), FL+CBT ($t = 8,41$, $df = 28$, $p < 0.0001$), PL+CBT ($t = 8,17$, $df = 32$, $p < 0.0001$) and CBT ($t = 6,21$, $df = 29$, $p < 0.0001$).

4.4.4 Montgomery Asberg Depression (MADRS)

Table 4.7 lists the mean scores on the MADRS for each group at each assessment point.

Two factor analysis of variance on MADRS scores over the wash-in period (Day -7 to Day 0) revealed a significant effect for time only ($F (1,144) = 61.06$, $p < 0.001$) indicating that all five groups showed a significant reduction in MADRS scores during wash-in. Between group analysis on MADRS scores during the entire treatment period revealed a significant group ($F (4,142) = 3.22$, $p < 0.01$), time ($F (3,426) = 103.31$, $p < 0.001$) and interaction effect ($F (12,426) = 5.11$, $p < 0.001$) indicating differential changes between groups.

Table 4.7 Means and standard deviations (s.d.) for Montgomery Asberg Depression Rating Scale (MADRS) for all groups at each assessment point during treatment.

MADRS	FL	PL	FL+CBT	PL+CBT	CBT
DAY -7	13.5	14.6	13.8	14.2	14.0
	(4.6)	(4.2)	(3.9)	(3.6)	(4.1)
DAY 0	11.8	13.2	12.1	11.9	12.6
	(4.7)	(4.3)	(4.3)	(4.1)	(5.4)
DAY 42	8.2	13.1	6.8	7.7	7.0
	(6.5)	(9.0)	(6.1)	(7.4)	(4.3)
DAY 84	6.9	13.4	3.8	6.0	3.9
	(7.7)	(10.9)	(6.5)	(8.3)	(4.6)

Differences from the PL group were shown by the FL+CBT group at Day 42 ($p < 0.05$) and Day 84 ($p < 0.001$), the CBT group at Day 42 ($p < 0.05$) and Day 84 ($p < 0.001$) and the PL+CBT and FL groups at Day 84 only (both $p < 0.05$). There were no other between group differences. Comparison of pre- (Day 0) with post (Day 84) scores within groups revealed a significant reduction in MADRS scores throughout treatment for FL ($t = 5.13$, $df = 28$, $p < 0.0001$), FL+CBT ($t = 7.92$, $df = 28$, $p < 0.0001$), PL+CBT

(t = 4.46, df = 32, p < 0.0001) and CBT (t = 7.98, df = 29, p < 0.0001), but not for PL (t = 0.13, df = 27. n.s.).

4.4.5 Fear Questionnaire - Agoraphobia Scale (FQ - AG)

Table 4.8 lists the mean scores on the FG-AG for each treatment group at each assessment point. Between group analysis of variance for FQ-AG scores revealed a significant time (F (2,284) = 72.88, p < 0.001), and interaction effect (F (8,284) = 6.01, p < 0.001). The group effects did not reach significance. Significant differences existed between groups at Day 84 only when the FL+CBT, CBT, and FL groups differed significantly (all p < 0.05) from PL.

Table 4.8 Means and standard deviations (s.d.) for Fear Questionnaire-Agoraphobia Scale (FQ-AG) for all groups at each assessment point during treatment.

FQ-AG	FL	PL	FL+CBT	PL+CBT	CBT
DAY 0	11.4	13.5	16.4	19.9	15.0
	(10.0)	(11.4)	(11.5)	(14.9)	(11.2)
DAY 42	8.0	12.3	6.9	10.2	7.0
	(8.8)	(11.7)	(8.8)	(10.6)	(5.5)
DAY 84	5.5	13.7	4.7	7.2	5.1
	(7.9)	(13.2)	(7.8)	(10.6)	(5.4)

The PL+CBT group did not differ significantly from PL at any point. Comparison of pre- (Day 0) with post- (Day 84) scores on the FQ-AG within groups showed a significant reduction throughout treatment for all treatment groups, (FL, t = 3.44, df = 28, p < 0.002; FL+CBT, t = 7.24, df = 28, p < 0.0001; PL+CBT, t = 5.99, df = 32, p < 0.0001; CBT t = 4.82, df = 29, p < 0.0001) with the exception of the PL group (t = 0.16, df = 27, n.s.).

4.4.6 Panic Attacks

The number and percentage of each treatment group who were free of major panic attacks at Day 84 were FL n = 20, 68.9%; PL n = 17, 60.7%; FL+CBT n = 24, 82.7%; PL+CBT n = 25, 75.7%; CBT n = 21, 70.0%. A more detailed analysis of panic data collected at all assessment points and including measures of panic attack and limited symptom attack frequency, severity and duration will be given in Chapter 6. Panic attacks were rated for one week prior to Day 84.

4.4.7 Clinical Significance of Outcome Results

The foregoing results are described entirely in terms of the statistical significance of change in treatment. It has been argued (Jacobson & Ravenstorf 1988, Jacobson & Truax 1991), that statistically significant results may nonetheless have little clinical relevance. Jacobson and colleagues argued for the further analysis of outcome data in terms of the clinical significance of change and suggest criteria of assessment. For measures where data is available for normal as well as clinical populations, a cut-off score for clinically significant change can be calculated, reflecting change from the clinical to the non-clinical population. Such a criterion was established for the FQ-Ag scores using the data collected on a non-clinical population by Mizes & Crawford (1988). A cut-off score of 8 or below indicated clinically significant change on this measure. Where data on a non-clinical population do not exist, Jacobson and Ravenstorf (1988) recommend a cut-off score for clinically significant change where a patient score falls outside the range of the dysfunctional population by two standard deviations from the pre-treatment mean of that population, in the direction of functionality. This criterion was employed with two measures, firstly the HAM-A, where it established a criterion of moderate severity (cut-off score of 12 or below) and secondly, with the SRT, where the variance in this measure gave rise to large standard deviations, and thus a highly stringent criterion of clinically significant change (cut-off score of 5 or below).

Table 4.9 Number (%) of patients in each group achieving criterion "clinically significant change" on HAM-A, SRT, and FQ-AG at Day 84.

	FL n = 29	PL n = 28	FL+CBT n = 29	PL+CBT n = 33	CBT n = 30
DAY 84					
Clinically significant change on :					
HAM-A	24	13	25	29	28
	(82.8)	(46.4)	(88.2)	(87.8)	(93.3)
SRT	8	5	16	14	12
	(27.6)	(17.8)	(55.2)	(42.4)	(40.0)
FQ-AG	24	14	24	24	23
	(82.8)	(50.0)	(82.8)	(72.7)	(76.7)

Table 4.9 reports the number of patients in each treatment group achieving clinically significant change at Day 84 on the HAM-A, SRT, and FQ-AG. All of the active treatment groups (FL, FL+CBT, PL+CBT, and CBT) had a large proportion of patients achieve clinically significant change on the HAM-A. Proportions of patients achieving clinically significant change on the more stringent criterion for the SRT were lower with only the FL+CBT group achieving clinically significant change in more than half the patients in that group. For the FQ-AG a substantial proportion of patients achieved clinically significant change with the FL+CBT, and FL groups achieving the highest proportion. On all measures the PL group showed the lowest proportion of patients achieving clinically significant change.

4.4.8 Follow-Up

Meaningful follow-up data can be difficult to collect and evaluate particularly in the primary care setting as patients may require or receive subsequent treatment between the end-point assessment and follow-up assessment. It is essential therefore to exclude from any follow-up analysis those patients who have received subsequent treatment during the follow-up phase.

All patients were requested to attend a 6 month follow-up appointment. Patients who had taken any psychotropic medication, regardless of quantity, or who had attended any appointments with psychologist, psychiatrist, or had any other secondary mental health referral during the follow-up period were deemed to have received follow-up treatment.

Table 4.10 illustrates the numbers in each treatment group who had received no follow-up treatment according to this strictly defined criterion. This number was highest for the FL+CBT group. Figures are also given for number of patients who failed to attend for follow-up, this proportion was highest for the CBT group. As no follow-up information was available on non-attenders they cannot be included in follow-up analyses.

Table 4.11 illustrates the numbers (and percentages) of patients in each treatment group who received no intervening treatment and who continued to achieve clinically significant change on the HAM-A, SRT and FQ-AG at 6 month follow-up. Overall the proportion of patients achieving clinically significant change in each group is lower than at end-point (Day 84). This is obviously partly due to the exclusion of patients who received intervening treatment and of those who failed to attend.

Table 4.10 Number (%) of patients in each group attending follow-up and number (%) receiving post study treatment at 6 month follow-up

	FL	PL	FL+CBT	PL+CBT	CBT
Completers sample n =	29	28	29	33	30
No. of follow-up attenders	23	21	24	30	28
	(79.3)	(75.0)	(82.8)	(90.9)	(93.3)
No. of follow-up attenders with no subsequent treatment	12	8	18	20	15
	(41.4)	(28.6)	(62.1)	(60.6)	(50.0)

Table 4.11 Number (%) of follow-up attenders in each group with no subsequent treatment who continue to achieve clinically significant change on HAM-A, SRT and FQ-AG at 6month follow-up.

	FL	PL	FL+CBT	PL+CBT	CBT
6 Month FU Clinically significant change on :					
HAM-A	11	8	18	18	15
	(37.9)	(28.6)	(62.1)	(54.5)	(50.0)
SRT	4	4	10	11	11
	(13.8)	(14.3)	(34.5)	(33.3)	(36.7)
FQ-AG	10	7	16	17	15
	(34.5)	(25.0)	(55.2)	(51.5)	(50.0)

A consistent pattern is observable, in that the groups who received psychological treatment (FL+CBT, PL+CBT, and CBT) showed a greater preservation of clinically significant change over follow-up from those receiving medication alone (FL and PL).

4.5 Discussion

At end-point assessment all of the active treatment groups (FL, FL+CBT, PL+CBT, and CBT) showed statistically significant improvement on all measures. There were no statistically significant differences between active treatment groups on any measures during treatment. The overall impression therefore, is one of equal improvement following treatment with either fluvoxamine alone, fluvoxamine or placebo in combination with cognitive behaviour therapy, and with cognitive behaviour therapy used alone. This pattern of equal efficacy amongst active treatments has been noted for

previous outcome studies (Kazdin & Bass 1989). However, a closer inspection of the pattern of results and levels of clinically significant change, indicates qualitative differences between groups in treatment response and over follow-up. The placebo group (PL) showed statistically significant change in treatment on the HAM-A and SRT only with 60.7% of this group being free from major panic attacks at Day 84. These reductions in therapist and patient rated anxiety and panic frequency indicate a relatively strong placebo response in this study and it is against this response that the improvement in the active treatment groups is compared statistically. The placebo group also evidenced the lowest proportions of patients achieving clinically significant change on the HAM-A, SRT, and FQ-AG. This overall picture of poor outcome is further reinforced by results at follow-up where the placebo group showed the lowest number of patients who had received no additional treatment during the follow-up period.

Patients receiving fluvoxamine (FL) showed significant gains in treatment pre- post on the HAM-A, SRT, and FQ-AG. These gains were statistically significantly different from patients receiving placebo (PL) on the HAM-A, from Day 42 onwards. Of patients in the FL group, 67% (n = 20) were free from major panic attacks at end-point, Day 84. It is reasonable to conclude from this pattern of results that the drug fluvoxamine was statistically more effective than placebo in the treatment of panic disorder and agoraphobia, and that this advantage appeared from mid-point (Day 42) in treatment on the HAM-A and between mid-point and end-point (Day 84) on the other measures. These findings of statistical significance are further reinforced when clinical significance is considered. The FL group showed a high proportion of patients (82.8%, n = 24) achieving clinically significant change on the HAM-A, and an equal proportion (83.0%, n = 24) achieving such change on the FQ-AG. Indeed, this was the highest proportion of clinically significant change on the FQ-AG (equal to that of the FL+CBT group).

The FL group showed a smaller proportion of patients achieving clinically significant change on the patient rated measure of anxiety, SRT, than on the HAM-A and FQ-AG, with only 27.6% (n = 8) of patients achieving this status.

Results for the FL group were not entirely unequivocal. Scores on the patient-rated measure of anxiety, SRT, for the FL group were statistically different from the PL group on one occasion only at Day 56. Results from the follow-up of the FL group showed that 41.4% (n = 12) of patients in this group had received no additional treatment during the follow-up phase. This figure was higher than that of the PL group (28.6%, n = 8) but

lower than those for the groups receiving either fluvoxamine or placebo plus CBT (FL + CBT, PL + CBT) or CBT alone.

Patients receiving cognitive behaviour therapy alone (CBT) showed statistically significant improvement pre-post on all the target measures (HAM-A, SRT, FQ-AG). These improvements were statistically significantly different from the placebo (PL) group on the HAM-A from Day 42 onwards and the FQ-AG at Day 84. At end-point (Day 84) 70.0% (n = 21) of the CBT group were free from major panic attacks. As for other treatment groups, improvements on the patient rated anxiety measure, SRT, were less robust, with scores on this measure being statistically significantly different from the PL group on two occasions only, at Day 56 and at end-point, Day 84. These results attest to the overall efficacy of this psychological treatment used without any adjunctive psychotropic medication in the treatment of panic disorder and agoraphobia. This finding is significant, given the relative scarcity of studies of psychological treatments for panic disorder carried out on medication-free populations (Power & Sharp 1995).

The statistical significance of improvements in the CBT group are again reinforced by the findings on clinical significance of change. The CBT group achieved the highest proportion of patients (93.3%, n = 28) achieving clinically significant change on the HAM-A. As with other groups the proportion of patients achieving the more stringent criterion of clinically significant change on the SRT was lower (40.0%, n = 12). Of the individual treatments (FL, PL, CBT) the CBT group showed the strongest and most comprehensive response. The CBT treatment did, however, show a higher drop out rate (32.2%, n = 13) than the other treatment groups. Since the majority of CBT patients lost to treatment did not return for treatment termination assessment, we cannot be sure of the reasons for their drop out. Similar drop out rates (circa 20-25%) from psychological treatments were, however, found for panic disorder patients in a series of studies by Michelson and colleagues (Michelson et al 1985, 1990) using graded therapist assisted exposure and programmed practice, and by Black and colleagues (Black et al 1993a) using cognitive therapy. Interestingly, these are the only other reports of drop out rates from psychological treatments given in the controlled absence of concurrent psychotropic medication.

Patients in the PL+CBT group showed statistically significant improvements pre-post on all target measures, (HAM-A, SRT, FQ-AG). These improvements were statistically significantly different from the placebo (PL) group from Day 42 onwards on the HAM-A.

The PL+CBT group differed from the PL group on the patient rated SRT on three occasions at Day 42, Day 56, and Day 84, again reflecting the more volatile results from this scale. At end-point (Day 84) 75.7% (n = 25) of the PL+CBT group were free from major panic attacks. The PL+CBT group failed to show a significant difference from PL on the FQ-AG. This suggests that although the PL+CBT treatment showed a statistically significant improvement in rated agoraphobic avoidance pre-post, the combination of placebo plus cognitive behaviour therapy did not produce improvements statistically significantly greater than those achieved by using placebo medication plus therapist contact. The drop-out rate for patients receiving CBT alone, however, was higher than for placebo + CBT.

Results assessed in terms of clinical significance suggest a general equivalence for the CBT and PL+CBT groups although the CBT group did produce slightly higher proportions of patients achieving clinically significant change on the HAM-A and FQ-AG. Over follow up, the PL+CBT group showed a proportion of patients receiving no post study treatments which at 60.6% (n = 20) was similar to that for the other combined treatment group FL+CBT, (62.1%, n = 18). The proportion of patients achieving clinically significant change on the target measures (HAM-A, SRT, FQ-AG) surviving to 6 month follow up with no subsequent treatment was also similar to that for the other groups receiving CBT (CBT and FL+CBT) and higher than that for the group receiving medication without active psychological treatment. This suggests that cognitive behaviour therapy whether used alone or in combination with fluvoxamine or placebo, enhances the maintenance of treatment gains over 6 month follow up.

As with all the other active treatment groups the FL+CBT group showed statistically significant improvements pre-post (HAM-A, SRT, FQ-AG). These improvements were all statistically significantly different from placebo (PL). The FL+CBT and CBT groups were the only groups to show statistically significant differences from placebo on all target measures. The FL+CBT group showed statistically significant differences from placebo earlier than any other group with differences on the HAM-A and the SRT differing significantly from Day 28 onwards. The FL+CBT group was the only active treatment group to show a statistically significant difference from the PL group on the patient rated measure of anxiety, SRT, at all assessment points from Day 28 onwards. At end-point 82.7% (n = 24) of the FL+CBT group were free from major panic attacks, the largest proportion of all the treatment groups. Thus the active combination treatment, FL+CBT can be seen to have resulted in the most robust treatment gains with significant

gains being noticeable earlier in treatment than for the other active treatment groups. The FL+CBT group showed some advantage over other treatment groups in terms of clinically significant change, achieving the largest proportion of patients (55.0%, n = 16) to achieve this criterion on the SRT. These findings carried over into follow-up with this group having the largest proportion of patients noted to have required no subsequent treatment (62.1%, n = 18). It is reasonable to conclude, therefore, that the active combination treatment, FL+CBT, produced the most robust treatment response showing the earliest significant differences from the PL group.

Overall, the absence of statistically significant differences between the active treatment groups (FL, CBT, PL+CBT, FL+CBT), initially suggested therapeutic equivalence. When clinical significance was investigated, however, and compared with that of the placebo group (PL), differences emerged between treatment groups that were suggestive of differing therapeutic potency. The two treatment groups providing the most consistent treatment response were the CBT group, and the FL+CBT group, with the latter showing gains earlier in treatment.

When considering these findings there are problems with the present study that should be borne in mind. A single therapist (DS) carried out all treatments and outcome results may therefore reflect factors associated with the presentation of treatments by this therapist rather than factors associated with the treatments themselves. The present study did not employ any biochemical assessments of either levels of study medication or as a screen for the use of non-permitted concurrent psychotropic medication, as this was found to be logistically impractical due to the study being conducted in a primary care setting rather than a central specialist clinic. Compliance with study medication was assessed via return pill counts and use of non-permitted medication by interview at each assessment session. Whilst these methods are less reliable than biochemical assay a small number of exclusions from analysis were made on each criterion (n = 4 and n = 2, respectively).

An attempt has been made in this study to balance therapist contact across all treatment groups, thus patients receiving FL or PL alone had appointments of equivalent duration to those for patients in the CBT groups. This being the case the superiority for the CBT groups found here cannot be attributed solely to the increased therapist contact that CBT entails. The balance for therapist contact employed in this study has however meant that the drug alone groups received appointments which were significantly longer than those employed in standard

general practice. As such the FL and PL groups in this study may not be truly representative of these treatments as actually employed in the primary care setting. To rectify this a study is required employing a further two groups of patients given FL or PL alone to an identical schedule of contact to this study with the exception of duration of appointment which would be reduced to 5-10 minutes. This would constitute a more realistic test of the performance of the drug alone treatments in primary care. Another aspect of the current study worthy of comment also relates to therapist contact. All of the treatment groups in this study were seen on nine occasions (including initial assessment, but excluding follow-up). This is substantially fewer treatment sessions than the 12-16 sessions employed in previous studies of CBT in the treatment of panic disorder and agoraphobia (Shear et al 1991, Clark et al 1994). The CBT employed in the current study might reasonably be referred to as brief CBT. The findings of strong efficacy for this shorter duration CBT in the treatment of panic disorder and agoraphobia is therefore of potential relevance to the management of this prevalent condition in primary care.

Regarding the assessments employed in this study, results for panic attacks were quoted as percentages or patients in each group free from major panic attacks at treatment end point only. Whilst this is the panic measure common to most previous studies, no information is provided on other possible panic variables such as limited symptom attack frequency and panic intensity and duration. Emphasis was also placed on the primary care setting of the study and yet the measures employed were all complex and time-consuming rating scales which may not lend themselves to use as outcome measures in this setting (King 1997). Both of these issues warrant further investigation and will be addressed in Chapter 5 and Chapter 6. The follow up data from this study also present some problems. The use of strict criteria for post-study treatment, namely any psychotropic medication use, and any psychology, psychiatry, or other mental health attendance may well have served to depress the size of follow up samples in this study. This was considered to be preferable to the procedure wherein post-study treatments are not given sufficient attention. Indeed, "treatment free" follow up results are quoted for samples where a proportion of patients had been taking concurrent psychotropic medication during the study period, and presumably over follow up also (Clark & Ehlers 1993, Chambless & Gillis 1993). Follow-up results were also affected by the lack of information available for patients who defaulted on follow-up appointments. The question

of maintenance of gains post-treatment is of considerable clinical relevance, given the finding that patients with panic disorder and agoraphobia make heavy demands on primary care resources prior to treatment (Simpson et al 1994). Further assessment of patients patterns of treatment use post-study may therefore be important.

In summary, the present study suggests that fluvoxamine does produce gains in the treatment of panic disorder and agoraphobia when compared with placebo. There is however some fall-off in these gains over follow-up. Cognitive behaviour therapy also produces gains in treatment that are better maintained over follow-up. The use of a placebo plus cognitive behaviour therapy combination appeared generally less effective in comparison with placebo than did cognitive behaviour therapy used alone. This is in keeping with the prediction of Hollon & DeRubies (1981) that placebo plus psychotherapy combinations are likely to underestimate the effectiveness of the psychotherapy. The gains produced by cognitive behaviour therapy used alone in the controlled absence of concurrent psychotropic medication were slower to emerge than those for the group receiving the active treatment combination of fluvoxamine plus cognitive behaviour therapy. In all cases, any significant improvement over placebo was not evident until after four weeks of treatment, this suggesting that the treatments employed in this study required some time to bring about significant change.

Clinically, the results of this study suggest that cognitive behaviour therapy provides an effective, treatment for panic disorder and agoraphobia, which may be enhanced by the addition of the selective serotonin reuptake inhibitor, fluvoxamine. The exact mechanism underlying clinical change in these treatments, used either alone or in combination, remains unclear, but should be the focus of future research effort. The present study has also been reported in detail by Sharp et al (1996).

CHAPTER 5 GLOBAL MEASURES STUDY

5.1 Introduction

Studies investigating the relative and combined efficacies of pharmacological and psychological treatments for panic disorder, have been conducted primarily in specialist university clinics or hospital settings despite the bulk of morbidity in panic disorder and agoraphobia being encountered in general practice (Ashcroft et al 1987, Katerndahl & Realini 1995). The applicability of these previous treatment outcome studies to the majority of patients seen and treated solely in primary care settings is questionable (Wilkinson & Lewis 1990).

Treatment outcome in clinical trials has generally been reported as percentages of patients free of major panic attacks at treatment end-point, although the reliability of this measure has been questioned (Shear & Maser 1994). Outcome has also been reported in terms of patient rated questionnaires, such as the Fear Questionnaire (Marks & Mathews 1979), which concentrates principally on avoidance behaviours and thus represents only a partial assessment of the clinical presentation of panic disorder and agoraphobia. This problem has been rectified in some studies (Marks et al 1993, Clark et al 1994, Ost et al 1993) by the use of therapist rated anxiety scales, often the Hamilton Anxiety Scale (Hamilton 1959). The use of such scales is time consuming and therefore they may not be easily employed in primary care settings (King 1977). Whilst reductions pre- to post-treatment on such scales may achieve statistical significance they do not, in the absence of comparative normative data, give a clear indication of the clinical significance of any improvement, nor do they indicate whether any improvement noted is accompanied by significant improvements in the patient's general wellbeing and social functioning.

As outlined in Chapter 2, there is a need for more brief global assessment measures in clinical trials of pharmacological and psychological treatments for panic disorder which are applicable for use in primary care settings, and which provide information useful to the management of panic disorder patients. Some studies have employed global measures of outcome but have used different measures for therapist and patient thus making comparison impossible (Michelson et al 1990, Shear et al 1991). Others have employed global measures for therapist only (Black et al 1993a). Only one study to date has employed the same global outcome measure for therapist and patient however no comparison of ratings was made (Marks et al 1993). Only

two studies have employed measures of the impact of treatment on patient's level of social functioning (Marks et al 1993, Black et al 1993a). This is a considerable omission given that one of the main aims of treatment for panic disorder and agoraphobia is to increase patients level of social functioning and facilitate a return to a more normal lifestyle. Furthermore none of the previous studies that included global measures made any comparison between outcome as assessed on these measures and on the more complex standardised scales also employed. A demonstration of concordance between these global measures and the more complex standardised measures is required to establish the validity of the global measures.

Chapter 4 reported the results of a treatment outcome study comparing pharmacological and psychological treatments for panic disorder and agoraphobia. The study was conducted in the primary care setting and outcome was reported in terms of detailed and complex research focused measures. The present study reports the outcome of the same treatment study using brief global measures of outcome completed by therapist, patient, and referring general practitioner, along with brief patient self-report measures of general wellbeing and social functioning. All of these measures were selected to be shorter and less time consuming to complete than the more research oriented and standardised measures more commonly used in research outcome studies. Thus the measures reported in the present Chapter were selected to be more "user friendly" and therefor more applicable to use in routine general practice. If demonstrated to be viable, these brief global ratings would show promise as quick and easy outcome measures suitable for use in routine clinical audit.

5.2 Method

5.2.1 Subjects

The patients in this study were those treated in the main study reported as Chapter 4. All patients were referred by general practitioners (GP) and were those considered suitable for pharmacological and/or psychological treatment. Patients were seen for all appointments in their local GP clinic. Following initial GP assessment and referral patients were seen by a clinical psychologist for semi-structured interview to ascertain patient characteristics, presenting condition, and severity of illness.

5.2.2. Inclusion criteria

Inclusion criteria were those employed in the main treatment outcome study and are reproduced in detail elsewhere (Sharp et al 1996, Chapter 4). Main inclusion criteria were: panic disorder with or without agoraphobia conforming to Diagnostic and Statistical Manual of Mental Disorders Third Edition - Revised (DSMIII-R, 1987) criteria; a minimum score of 15 on the Hamilton Anxiety Scale (Hamilton 1959); a maximum score of 20 on the Montgomery Asberg Depression Rating Scale (Montgomery & Asberg 1979); symptoms which had lasted three months or longer; no psychotropic medication in the 28 days prior to entry and throughout the study treatment period; aged between 18 and 70 years inclusive.

Over three years 238 patients were referred by GPs, of these 193 entered the study. Analysis was conducted on a sample of 149 completers and defined completers. Patients were randomly allocated to one of five treatment groups; fluvoxamine (FL) (n = 29), placebo (PL) (n = 28), fluvoxamine plus cognitive behaviour therapy (FL+CBT) (n = 29), placebo plus cognitive behaviour therapy (PL+CBT) (n = 33), and cognitive behaviour therapy (CBT) (n = 30). Demographic details of the sample have been given in detail previously (Sharp et al 1996, Chapter 4).

5.2.3.Treatments

All patients were seen to an identical schedule of contact and received either fluvoxamine, placebo, fluvoxamine plus cognitive behaviour therapy (CBT), placebo plus CBT, or CBT alone. Treatment specifications and schedules of contact were those of the main study and are described in more detail elsewhere (Sharp et al 1996, Chapter 4).

5.2.4. Procedure

Following assessment and referral by their GP, patients were seen by the psychologist therapist for initial assessment (Day -7) when they were randomised to treatment groups. Over the 12 week treatment period all patients received treatment to an identical schedule of contact with treatment appointments at Day -7, 0, 7, 14, 28, 42, 56, 70 and 84. Pre, and post treatment assessments for the present study

were conducted at days -7, and 84. Patients were also seen for follow-up at 6 months. Individual appointments lasted a minimum of 30 and a maximum of 60 minutes with all groups receiving an approximately equivalent amount of therapist contact.

5.2.5. Measures

(a) Severity of illness: was measured using the Global Symptom Severity Scale (Guy 1976). This seven-point scale, designed to rate outcome in psychopharmacological research, gives a range of clinical severity from 1 `normal' to 7 `extreme'. This scale was completed by the psychologist therapist, and referring GP at Day -7 and Day 84.

(b) Change in symptoms: was measured using the Clinical Global Improvement Scale (Guy 1976). This seven-point scale, designed with the same aim as above, rates symptom change on a range of 1 `very much improved' to 7 `very much worse', was completed by the psychologist therapist, referring GP, and patients at Day 84.

(c) The General Health Questionnaire (GHQ, Goldberg 1978) was used to provide an overall self-rated measure of psychiatric wellbeing, with results reported as total scores. The 60 item version of the scale was completed by patients at Day 0 and Day 84.

(d) The Sheehan Disability Scale (SD, Sheehan 1986) is a simple measure of social functioning which assesses disruption to daily lifestyle and comprises three 10 point subscales where patients self-rate disruption to work, social life, and family/home life completed by patients at Day 0 and Day 84. Copies of measures are given in Appendix II.

5.3. Results

5.3.1. Statistical Analysis

Repeated measures analysis of variance with a between subjects factor, treatment group, and a within subjects factor, assessment point, were conducted, with simple effects one-way analyses of variance to investigate significant results. Further post hoc analysis was conducted using defined contrasts to investigate differences between drug and placebo groups, both with CBT (FL, FL+CBT vs. PL, PL+CBT) (1 -1 1 -1 0) and without CBT (FL vs. PL) (1 -1 0 0 0) and those groups employing cognitive behaviour therapy with those not employing this treatment (FL, PL vs. FL+CBT, PL+CBT, CBT) (3 3 -2 -2 -2). The particular defined contrasts chosen were decided prior to the analysis of the present data, and following consideration of the pattern of findings obtained with the more complex measures used in the main study (Sharp et al 1996, Chapter 4). Within group comparisons of ratings before and after treatment were carried out using paired two-tailed t-tests.

5.3.2. Severity of Symptoms

Table 5.1 presents the mean ratings and statistical analyses of Global Symptom Severity before (Day -7) and after (Day 84) treatment by the psychologist therapist.

For psychologist therapist ratings of symptom severity, analysis of variance revealed significant group ($F(4,144) = 5.16$, $p < 0.001$), time ($F(1,144) = 389.91$, $p < 0.0001$) and interaction ($F(4,144) = 10.98$, $p < 0.0001$) effects indicating differential changes between groups. No significant differences existed between groups before treatment (Day -7) where the largest proportion of patients for each group fell in the "moderate" or "marked" categories. Differences had emerged by Day 84 with 73%-80% of patients in the groups, including CBT (FL+CBT, PL+CBT, CBT) in the "normal/borderline" categories compared to 55% for FL and 29% for PL. Defined contrasts confirmed this finding, there being a significant interaction between group and symptom severity score after treatment ($F(1,144) = 9.98$, $p < 0.0001$). The contrast comparing the groups including CBT with those which did not was significant, ($p < 0.0001$), as was that comparing FL with PL, both without CBT, ($p < 0.0001$), and with CBT ($p < 0.001$). The contrast comparing all four drug groups with CBT alone i.e. (1111 -4) was also significant ($p < 0.01$). All five treatment

groups showed a significant reduction in symptom severity scores over treatment ($p < 0.01$ and above).

Table 5.1 One-way ANOVAs, t-tests, and Means (s.d.) for psychologist and GP ratings of Global Symptom Severity for each group pre and post treatment.

	FL	PL	FL+CBT	PL+CBT	CBT	F
Psychologist Global Symptom Severity						
PRE (Day -7)	4.34 (0.77)	4.14 (0.76)	4.28 (0.65)	4.42 (0.79)	4.16 (0.87)	0.71 n.s.
POST (Day 84)	2.28 (1.22)	3.46 (1.48)	1.72 (1.06)	2.03 (1.33)	1.70 (0.95)	9.98****
t	10.13****	2.64**	11.07****	11.02****	10.34****	
GP Global Symptom Severity						
PRE (Day -7)	4.34 (0.72)	4.43 (0.84)	4.59 (0.78)	4.27 (0.84)	4.46 (0.90)	0.65 n.s.
POST (Day 84)	4.10 (3.47)	5.29 (2.99)	4.24 (3.61)	4.51 (3.17)	4.47 (3.37)	0.53 n.s.
t	0.38 n.s.	1.66 n.s.	0.51 n.s.	0.43 n.s.	0.01 n.s.	

** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, n.s. not significant.

GP's ratings of mean severity of Global Symptom Severity before and after treatment are also given in table 5.1. Analysis of variance indicated no significant differences between groups on GP ratings of symptom severity both before and after treatment. Within group analysis indicated no significant change in GP CGI during treatment, and few notable differences between groups in the proportions of patients allocated to the categories of severity of symptoms before (Day 0), and after treatment (Day 84).

GP's ratings of Global Symptom Severity showed a weak but significant relationship with psychologist's rating of Global Symptom Severity using both pre treatment (Pearson r = 0.27, $p<0.01$), and post treatment (Pearson r = 0.26, $p<0.01$) scores. There was therefor little agreement between referring GPs and the psychologist as to global severity of symptoms either before or after treatment.

5.3.3. Clinical Global Improvement

Means, standard deviations, and statistical analyses for the change in patients symptoms rated on the Clinical Global Improvement scale by psychologist therapist, GP and by patients themselves are given in Table 5.2.

Table 5.2 One-way ANOVAs, and Means (s.d.) for GP, Psychologist, and Patient ratings of Clinical Global Improvement for each group post treatment (Day 84).

	FL n = 29	PL n = 28	FL+CBT n = 29	PL+CBT n = 33	CBT n = 30	F
GP Clinical Global Improvement	3.93 (3.52)	4.85 (3.35)	3.93 (3.71)	4.03 (3.39)	4.06 (3.61)	0.35 n.s.
Psychologist Clinical Global Improvement	2.27 (1.71)	2.93 (1.30)	1.37 (0.68)	1.82 (1.07)	1.60 (0.72)	8.11***
Patient Clinical Global Improvement	2.27 (2.08)	2.92 (1.80)	1.34 (0.85)	1.69 (1.57)	1.53 (0.68)	5.33***

** = $p< 0.01$, *** = $p< 0.001$, n.s. not significant.

Results for these measures were similar to those for Global Symptom Severity. There were significant differences between groups for change in symptoms rated by both psychologist therapist ($F(4,144) = 8.11$, $p < 0.001$) and patients ($F(4,144) = 5.33$, $p < 0.001$), but not for GP ratings. Defined contrasts comparing the drug alone groups (FL, PL) with those including CBT were significant for both psychologist therapist ($p < 0.0001$), and patients ($p < 0.001$), ratings. Psychologist therapist rated 85%-89% of patients in the CBT groups as "much improved/very much improved" compared to 75% for FL and 35% for PL. Similarly patients self-rated 88%-90% of the CBT groups as "much improved/very much improved" compared to 78% for FL and 48% for PL. The contrasts comparing drug with placebo were also significant for both psychologist therapist and patients ratings when drug alone groups were

compared without CBT, psychologist ($p < 0.001$), patient ($p < 0.001$), and with CBT, psychologist ($p < 0.0001$), patient ($p < 0.01$).

For psychologist therapist ratings the contrast comparing all four drug groups with CBT alone was also significant ($p < 0.05$).

The psychologist therapist and patients ratings of change in symptoms following treatment showed considerable agreement (Pearson $r = 0.89$, $p < 0.01$), whereas relationships were weaker between psychologists and GP ratings of change of symptoms (Pearson $r = 0.21$, $p < 0.01$), and GP and patient ratings (Pearson $r = 0.18$, $p < 0.05$).

5.3.4. General Health Questionnaire

Table 5.3 gives the means, standard deviations, and statistical analyses for total GHQ score before and after treatment.

Analysis of variance revealed significant group ($F(4,144) = 2.64$, $p < 0.05$), time ($F(1,144) = 68.51$, $p < 0.0001$) and interaction ($F(4,144) = 2.58$, $p < 0.05$) effects, indicating differential changes between groups. No differences existed between groups before treatment. Significant differences between groups emerged after treatment (Day 84), ($F(4,144) = 6.38$, $p < 0.0001$). Defined contrasts again yielded an identical pattern to previous measures with a superiority in GHQ scores for CBT groups over drug alone groups ($p < 0.0001$), and a superiority of FL over PL both with CBT ($p < 0.01$) and without CBT ($p < 0.01$). The contrast comparing CBT alone with all four drug groups was also significant ($p < 0.05$). Comparison of before (Day 0) with after (Day 84) treatment scores showed a significant reduction in GHQ scores for all groups with the exception of placebo.

Table 5.3 One-way ANOVAs, t-tests, and Means and standard deviations (s.d.) for GHQ and Sheehan Disability Scale before and after treatment

	FL n = 29	PL n = 28	FL+CBT n = 29	PL+CBT n = 33	CBT n = 30	F
GHQ						
PRE	19.56	22.82	19.93	19.78	21.47	0.21
(Day 0)	(17.35)	(17.29)	(16.79)	(15.95)	(16.39)	n.s.
POST	8.17	19.39	4.55	5.94	3.97	6.38****
(Day 84)	(14.50)	(20.25)	(11.88)	(10.95)	(6.43)	
t =	3.42**	0.84 n.s.	5.28****	4.76****	5.19****	
Sheehan Disability Scale						
Work:						
PRE	4.66	4.64	5.24	5.46	4.80	0.39
(Day 0)	(3.23)	(3.13)	(3.35)	(3.23)	(3.42)	n.s.
POST	2.24	4.29	1.38	2.10	1.87	4.36**
(Day 84)	(2.85)	(3.13)	(2.77)	(2.58)	(2.64)	
t =	3.86***	0.61 n.s.	5.74****	5.11****	4.32****	
Social Life						
PRE	5.03	5.18	6.97	6.12	5.73	0.75
(Day 0)	(2.76)	(3.72)	(2.92)	(3.43)	(2.86)	n.s.
POST	2.24	4.57	1.31	2.24	1.70	6.11****
(Day 84)	(2.76)	(3.23)	(2.25)	(2.92)	(2.37)	
t =	5.86****	0.85 n.s.	8.52****	5.84****	8.08****	
Home Life						
PRE	4.03	5.57	5.17	5.39	4.60	1.30
(Day 0)	(2.84)	(3.20)	(2.78)	(3.21)	(2.90)	n.s.
POST	1.93	4.04	1.00	1.46	1.60	6.12****
(Day 84)	(2.87)	(3.34)	(2.09)	(2.12)	(2.22)	
t =	4.39****	2.73**	8.01****	7.09****	4.99****	

** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, n.s. not significant.

Comparison of before (Day 0) with after (Day 84) treatment scores showed a significant reduction in GHQ scores for all groups with the exception of placebo.

5.3.5. Sheehan Disability Scale (SD)

The means and standard deviations for scores on this scale before and after treatment are also given in Table 5.3. Analysis of variance for the work scale revealed a significant time ($F(1,144) = 79.18$, $p < 0.001$) and interaction (group x time) ($F_{(4,144)} = 4.20$, $p < 0.01$) effect. The social life scale also revealed significant time ($F(1,144) = 146.41$, $p < 0.001$) and interaction ($F_{(4,144)} = 7.13$, $p < 0.001$) effects. The home/family life scale gave significant group ($F(4,144) = 2.95$, $p < 0.05$) time ($F(1,144) = 144.79$, $p < 0.0001$) and interaction ($F_{(4,144)} = 4.26$, $p < 0.01$) effects.

All groups, except PL, showed a significant reduction in scores on work (all $p < 0.001$) and social life (all $p < 0.0001$). All groups including PL showed a significant reduction in home/family life scores ($p < 0.01$ and above).

Differences existed between groups at Day 84 on work ($F(4,144) = 4.36$, $p < 0.01$), social life ($F(4,144) = 6.12$, $p < 0.0001$) and home/family life ($F(4,144) = 6.11$, $p < 0.0001$).

Defined contrasts showed an identical pattern to previous measures. The CBT groups were superior to the drug alone groups for work ($p < 0.01$), social life ($p < 0.0001$), and home/family life ($p < 0.0001$). Contrasts also revealed a superiority of FL over PL, without CBT for work ($p < 0.01$), social life ($p < 0.01$), and home/family life ($p < 0.01$). Results were similar for the comparison including CBT, work ($p < 0.01$), social life ($p < 0.001$), and home/family life ($p < 0.01$).

5.3.6. Further Analysis

Results presented thus far indicate that the global measures in this study were able to detect clinical changes in the active treatment groups. Results have also highlighted a considerable difference in acuity between psychologist and patient ratings on the one hand and GP ratings on the other. It is not clear as yet whether GPs or psychologist and patients ratings more accurately reflect patients clinical presentation as measured by the more complex measures employed in the main study (Chapter 4). This was investigated using correlations to assess the strength of

relationship between the global ratings (Global Symptom Severity and Clinical Global Improvement) and the standardised measures of outcome (HAM-A, SRT, and FQ-AG), employed in the main study (Sharp et al 1996, Chapter 4). Means, standard deviations, and analyses for the HAM-A, SRT and FQ-AG are given in Table 5.4, the correlations are given in Table 5.5.

Table 5.4. One-way ANOVAs, t-tests, and Means (s.d) for HAM-A, SRT, and FQ-AG for each group pre and post treatment

	FL n = 29	PL n = 28	FL+CBT n = 29	PL+CBT n = 33	CBT n = 30	F
HAM-A						
PRE (Day -7)	21.3 (3.7)	21.4 (4.5)	21.4 (3.6)	22.0 (4.2)	19.8 (3.6)	1.30 n.s.
POST (Day 84)	7.9 (7.0)	13.9 (8.9)	4.8 (5.7)	6.5 (6.7)	4.9 (4.4)	9.24****
t =	10.19****	4.09***	15.28****	14.5****	13.88****	
SRT						
PRE (Day -7)	33.5 (17.2)	38.4 (18.2)	33.0 (15.5)	33.9 (14.3)	33.5 (16.6)	0.51 n.s.
POST (Day 84)	16.2 (17.1)	30.2 (23.1)	10.3 (16.3)	13.3 (15.2)	13.9 (12.2)	5.93***
t =	4.96***	2.61**	8.41****	8.17****	6.21****	
FQ-AG						
PRE (Day 0)	11.4 (10.0)	13.5 (11.4)	16.4 (11.5)	19.9 (14.9)	15.0 (11.2)	2.16 n.s.
POST (Day 84)	5.5 (7.9)	13.7 (13.2)	4.7 (7.8)	7.2 (10.6)	5.1 (5.4)	4.95***
t =	3.44***	0.16 n.s.	7.24****	5.99****	4.82****	

** = p< 0.01, *** = p< 0.001, **** = p< 0.0001, n.s. not significant.

Table 5.5. Correlations (Pearson r) between post treatment scores on HAM-A, SRT, FQ-AG, GP and Psychologist Global Symptom Severity, and GP, Psychologist and Patient Clinical Global Improvement.

	HAM-A	SRT	FQ-AG
GP Global Symptom Severity	0.33**	0.35**	0.18*
GP Clinical Global Improvement	0.31**	0.32**	0.14 n.s.
Psychologist Global Symptom Seventy	0.95**	0.85**	0.70**
Psychologist Clinical Global Improvement	0.80**	0.72**	0.56**
Patient Clinical Global Improvement	0.76**	0.70**	0.51**

* = p< 0.05, ** = p< 0.01

GP Global Symptom Severity ratings correlated weakly with HAM-A, SRT and FQ-AG scores whereas psychologists Global Symptom Severity ratings correlated strongly with HAM-A, SRT and FQ-AG. Thus GP's ratings symptom severity were not strongly related to either the psychologist's ratings or to standardised measures of anxiety and avoidance. By contrast the psychologist's ratings of symptom severity were in close agreement with anxiety as measured by the HAM-A and SRT, and avoidance as rated on the FQ-AG.

A similar pattern emerged for GP, psychologist and patient Clinical Global Improvement, with GP ratings correlating weakly with HAM-A and SRT scores while the correlation with FQ-AG scores failed to reach significance. By contrast psychologist and patient ratings of Clinical Global Improvement showed strong correlations with HAM-A and SRT scores, whilst the correlations with FQ-AG scores tended to be slightly lower but remained statistically significant. Thus for improvement following treatment a greater degree of agreement between global ratings and standardised measures was found for psychologist and patient ratings than for GP ratings. It would appear therefor that GP's global ratings symptom severity and improvement following treatment did not accurately reflect the clinical picture as presented by psychologist and patient ratings and by standardised measures of anxiety and avoidance behaviours.

The lower correlations found with the FQ-AG indicate that this measure of agoraphobic avoidance behaviour was, in this study, a potentially a less sensitive indicator of global symptom severity, and in particular clinical global improvement than were the measures of anxiety (HAM-A, SRT).

5.4. Discussion

Outcome in the present study was assessed using brief global measures which are potentially more suitable for use in general practice. Results of the study indicate that these measures, despite their relative simplicity, are able to indicate differential outcomes between groups. Similar measures, in particular, psychologist and patient ratings have previously been shown to be sensitive to change in generalised anxiety disorder patients treated in primary care by either pharmacological or psychological interventions (Power et al 1990b).

All measures employed in the current study also gave virtually the same result, there being no disagreement between measures on the main pattern of findings. This again attests to the robustness of these relatively simple measures. As with any other rating measure, these global ratings do, however, rely on the accuracy of the raters used, as demonstrated by GP's ratings of symptom severity and global improvement. The GP's ratings were at variance with those of the psychologist and the patients themselves. This difference was further reinforced by the noticeably weaker correlations between GP ratings and the measures of anxiety and avoidance. A more forthright statement of the finding would be that GPs were unable to detect the large changes following treatment that were obvious to both the psychologist and the patients.

One possible explanation may be simply the length of time spent with the patients, and thus familiarity with the clinical picture. The psychologist had 9 appointments with each patient over a 13 week period, representing a maximum of 9 hours contact. The patients' familiarity with their own condition needs little elaboration. GPs, however, are unlikely to have had anything like the same amount of concentrated contact with the patients, and thus the accuracy of their assessments, as compared with those of the psychologist and the patients, may have been reduced as a result. It may also be the case that the GPs in the present study were insufficiently experienced in rating outcomes of panic disorder and agoraphobia. In the only previous study to employ GP ratings, (Power et al 1990b) the referring GPs were all members of a research group and had received training in research assessment methods. The Power et al (1990b) study found that GPs ratings were highly correlated with those of the psychologist. This would suggest that training of referring GPs might be required prior to their ratings being used in future studies.

If replicated in future studies, the lack of concordance with more complex outcome measures demonstrated by GP raters in this study would have relevance beyond the measurement of experimental treatment outcome. Researchers investigating, for example, service usage or number of drug prescriptions following an experimental treatment may have to be aware that such post study treatment would be likely to be provided by patient's GPs, and its provision would be informed by the GPs perception of treatment outcome, whether accurate or not.

Results obtained using these brief measures nonetheless indicated that all four active treatment groups (FL, FL+CBT, PL+CBT and CBT) were superior to the placebo (PL) group, but that those treatment groups which included CBT (FL+CBT, PL+CBT, CBT) showed a consistent and significant trend of superiority over fluvoxamine alone (FL). This pattern of outcome was found not only for the therapist and patient global rating scales, but also for the measures of general psychiatric wellbeing (GHQ) and for the ratings of social functioning (SD). These latter two measures indicated that the active treatments (FL, FL+CBT, PL+CBT, CBT) all brought about improvements in patients self-rated general wellbeing and social functioning, whereas the placebo (PL) group showed a significant improvement only on the home/family life subscale of the SD. This is an important finding suggesting that the improvements which did occur following treatment with placebo medication plus therapist contact despite being statistically significant on the measures of general anxiety employed in the main study (HAM-A, SRT), were not robust enough for the patients to feel any improvement in their general wellbeing or their functioning at work or socially. Obtaining patient ratings of changes in social functioning and general wellbeing following treatment might be regarded as an alternative method of assessing the clinical significance of the outcome of that treatment. These findings are of course of considerable relevance given that one of the main aims of treatment is to return patients to an acceptable level of social functioning. Taken in the light of this lack of improvement in wellbeing and social functioning, the report in Chapter 4, of only n = 8 (28.6%) of PL patients attending 6 month follow-up without having required further treatment, is easily understood.

Overall the findings of the present study are in agreement with those of the main study (Sharp et al 1996, Chapter 4) and reinforce the suggested efficacy for CBT either alone or in combination with fluvoxamine in the treatment of panic disorder and agoraphobia in primary care. Of further relevance to the primary care setting of the study, the brief measures employed in this study proved to be as discriminative and treatment responsive as the more complex measures used in the main study. Given the saving in time their use entails this is of potential relevance to the assessment of treatment outcome in primary care whether as a part of treatment outcome research or in the assessment or audit of everyday treatment efficacy. The findings for GP ratings would suggest, however, that some training of raters might

be required in future studies employing brief global measures of the type shown to be of value in the current study. The present study has been reported elsewhere as Sharp et al (1997b), and Sharp & Power (In Press).

CHAPTER 6 PANIC ATTACKS AS TREATMENT OUTCOME VARIABLES

6.1 Introduction

Panic attacks have been given a central role in the classification of panic disorder either with or without agoraphobia. The operationalisation and measurement of panic attacks is therefor an important part of any study investigating the efficacy of treatments for panic disorder and agoraphobia. The most widely used measure is panic attack frequency, indeed this aspect of panic attacks is embodied in DSM III, and DSM III-R as a defining factor in the classification of panic disorder. Panic frequency has commonly been assessed by asking patients to estimate the number of panic attacks they have experienced during a given time period, e.g. the last week or month. This method is included in diagnostic interviews such as the ADIS-R (Di Nardo et al 1983), and questionnaires such as the panic frequency subscale of the Mobility Inventory (Chambless et al 1985). In treatment studies, outcome is often expressed in terms of percentage of patients free of panic attacks at treatment end-point. The validity of panic-free status as a treatment outcome measure has been questioned (Shear & Maser 1994) particularly as it represents a single occasion measurement and therefor gives no indication of change in panic frequency during treatment. Percentage of patients panic free at treatment end-point has also been suggested to be a lenient measure of treatment efficacy which indicates treatment response more readily than other standardised outcome measures (Barlow 1988). The ability of panic free status to operate as a discriminative and informative treatment outcome measure might also be questioned, as it disregards the panic status of patients prior to the commencement of treatment. Thus a patient who suffered no panic attacks during the treatment period would be classified as a treatment responder using this measure, whereas another patient who had shown a notable reduction in panic attacks as a result of treatment but who experienced one further panic attack during the final assessment period would not. Investigation of the presenting features of panic attacks is necessary however firstly, to further understanding of the condition, and secondly to investigate how panic attacks change following treatment.

Studies investigating panic attack variables have had as their aim either the investigation of the phenomenology of panic attacks or, have employed panic attack

measures as outcome measures in treatment outcome studies. The phenomenological studies will be discussed first as their findings have potential ramifications for the measurement of panic as an index of treatment outcome.

The aim of phenomenological investigations has been to investigate the nature and pattern of the panic attacks suffered by panic disorder patients. The first finding of importance from these studies relates to the manner in which panic attacks are recorded. Three studies (Margraf et al 1987, Rapee et al 1990b, De Beurs et al 1992) compared the frequency of panic attacks in patient samples with panic frequency recorded both retrospectively and prospectively by using patient completed panic-monitoring diaries. All three studies found that frequency of panic attacks was exaggerated in retrospective report as compared to prospective continuous monitoring. This finding means that retrospective reports of panic attacks cannot be relied upon to provide an accurate indication of patients condition regarding panic attacks. Along with these three studies a further six studies (Street et al 1989, Krystal et al 1991, Basoglu et al 1992, De Beurs et al 1993, De Beurs et al 1994, Someya et al 1996) have investigated the phenomenology of panic attacks. All of these studies employed a prospective, event sampling method which requires patients to record details of any panic attack during or immediately after it's occurrence, thus avoiding the over-reporting bias found for retrospective reports. These studies have produced findings of relevance to clinical practice. Four studies have compared spontaneous and situationally triggered panic attacks and found few differences between them (Margraf et al 1987, Street et al 1989, Krystal et al 1991, Basoglu et al 1992) suggesting that differentiating between spontaneous and situational panic attacks may be unnecessary in clinical practice. Studies have also compared full DSM III/DSM III-R panic attacks, which must include 4 or more symptoms, and limited symptom attacks, which consist of 3 or fewer symptoms (Margraf et al 1987, Krystal et al 1991, De Beurs et al 1994). One study (Krystal et al 1991) found panic attacks produced higher ratings of severity than limited symptom attacks, whilst another (De Beurs et al 1994) found panic attacks to be of longer duration than limited symptom attacks. No other differences were found however, leading some researchers (Margraf et al 1987, Krystal et al 1991) to conclude that the distinction between panic attacks and

limited symptom attacks enshrined in DSM III-R and DSM IV has little diagnostic or clinical validity. This finding must be regarded as preliminary however as only one study (Krystal et al 1991) compared panic attacks with limited symptom attacks using a within-patients design. The other studies (Margraf et al 1987, De Beurs et al 1994) used a between subjects design, which assumes that all patients perceive and report the experience of panic in an equivalent way. Given the evidence suggesting considerable variation in reporting of panic attacks over time even within patients (Basoglu et al 1992, De Beurs et al 1994), this assumption is hard to justify. A within subjects comparison is therefor more appropriate, and further within subjects comparisons of panic attacks and limited symptom attacks are required. Such studies should include measures of panic severity and duration, as these have been shown to possibly differentiate panic attack and limited symptom attacks (Krystal et al 1991, De Beurs et al 1994), and may also have some utility as treatment outcome variables.

The above findings are relevant to the measurement of panic in wider clinical practice and suggest that panic should be assessed by prospective diary based monitoring and that it may not be necessary to distinguish between spontaneous and situational panic attacks. The inclusion of limited symptom attacks in any record of panic would seem to be important given that some evidence suggests more similarity than difference between panic attacks and limited symptom attacks (Margraf et al 1987, Krystal et al 1991). It is also suggested that any record of panic attacks should include measures of panic severity and duration. In order to assess the extent to which the above recommendations have been taken up in the assessment of panic in treatment outcome research a more detailed review of the measurement of panic in treatment outcome studies is required. To achieve this the treatment outcome studies reviewed in Chapter 2 were re-examined with particular regard to panic attack measurement. In the treatment outcome studies investigating psychological treatments (Table 2.1, Chapter 2), panic attacks were commonly assessed using prospective diary methods with only 3 of the 36 studies (Michelson et al 1990, Beck et al 1994, Lidren et al 1994) employing less reliable retrospective methods. Unfortunately other methodological inadequacies were more common. In many studies only panic attacks, as opposed to limited symptom attacks,

were recorded with patients being specifically briefed on the distinction prior to their recording their panic attacks. Given the lack of empirical evidence indicating any major distinction between panic attacks and limited symptom attacks this procedure is hard to justify. In other studies only panic frequency was recorded there being no measures of panic severity or duration. Severity and duration of panic attacks were recorded along with panic frequency in only six studies (Ost 1988, Barlow et al 1989, Telch et al 1993, Cote et al 1994, Bouchard et al 1996, Hecker et al 1996), but only two of these six studies (Ost 1988, Hecker et al 1996) actually reported results for severity and duration variables. Only one study (Telch et al 1993) included measures of panic attack and limited symptom attack frequency, severity and duration, unfortunately the data collected for limited symptom attacks in this study were not reported. Three of these six studies on psychological treatments failed to differentiate between treatments using panic attack frequency as an outcome variable (Barlow et al 1989, Cote et al 1994, Bouchard et al 1996), whilst a fourth (Hecker et al 1996) failed to differentiate between treatments using panic attack frequency, severity and duration. Only two studies found panic attack variables to differentiate between treatment groups at end-point. Ost (1988) found panic severity at treatment end-point significantly lower in their applied relaxation group than in the progressive relaxation group, while Telch et al (1993) found that panic attack frequency was significantly lower following group cognitive behaviour therapy as compared to a waiting list control group. Given the comparator this latter finding is hardly surprising. All six studies showed statistically significant pre to post treatment improvement in all panic variables used. It appears, in general, that the recording of panic attack data has been poor in psychological treatment outcome studies with very few studies including measures of severity and duration or including limited symptom attacks in their analyses. Furthermore, panic variables did not appear to strongly differentiate between competing treatments when employed as treatment outcome measures.

When treatment outcome studies comparing pharmacological with psychological treatments are considered the position is arguably worse. Of the 20 pharmacological vs. psychological treatment studies reviewed, (Table 2.2, Chapter 2) only six studies (Telch

et al 1985, Tobena et al 1990, Klosko et al 1990, Hegel et al 1994, Oehrberg et al 1995, De Beurs et al 1995) employed prospective measurements of panic attacks. In all the other studies the less reliable retrospective method was used. None of these six pharmacological vs. psychological treatment studies reported ratings of severity or duration, and the issue of panic attacks versus limited symptom attacks was rarely mentioned and was not specifically investigated in any study. Regarding treatment outcome, in two studies (Tobena et al 1990, Hegel et al 1994) the ability of panic variables to differentiate between treatments could not be assessed, as these were single treatment open trials. In a further two studies panic attack frequency did not differentiate between groups at treatment end-point (Telch et al 1985, Klosko et al 1990). The only significant differences between treatments in prospectively recorded panic attack variables in psychological vs. pharmacological treatment studies were found in the final two studies (De Beurs et al 1995, Oehrberg et al 1995) using non-parametric analyses of proportion of patients panic free at end point.

Overall it is clear that there is considerable variability in the quality of assessment of panic attacks in treatment outcome studies. The studies that have employed prospective methods have tended nonetheless to focus only on panic attack frequency failing to measure other potentially informative characteristics such as severity and duration of attacks. Limited symptom attacks are commonly excluded from analyses in psychological treatment studies and rarely mentioned in pharmacological vs. psychological treatment studies. Treatment outcomes in terms of panic attacks are most commonly expressed as proportions (usually percentages) of patients in a given treatment group panic-free at treatment end-point. Panic attack variables have rarely been employed as continuous measures throughout treatment and have consisted of pre-post difference or change in frequency of panic attacks. It is not clear as yet how valuable and discriminative a treatment outcome measure they may be. The value of panic frequency as an outcome measure was questioned in one study (De Beurs et al 1993) which employed treatments consisting of panic management techniques followed by the addition of in vivo exposure. Study results showed an increase in panic frequency when the exposure component of treatment was added making the panic frequency

variable less sensitive to overall change in treatment and at times difficult to interpret (De Beurs et al 1993). A final point concerns data configuration. The distributions found amongst the panic attack variables employed were mentioned in only three studies. Arntz & Van Den Hout (1996) noted that panic variables in their study were highly positively skewed and logarithmic transformations were employed to solve this problem. De Beurs et al (1995) also noted positively skewed distributions and consequently employed non-parametric analyses, as did Bouchard et al (1996) for their "non-normal" distributions. Distributions of data collected in all other studies were not mentioned and no corrective transformations or analyses described. Such are the flaws in previous research.

As panic attack variables are argued to be the core feature of the diagnostic classification of panic disorder, the main targets of clinical intervention, and the focus of many treatment outcome measures, the inconsistencies highlighted in the forgoing discussion suggest that more thorough and detailed investigation of panic attack variables in rigorously controlled outcome studies is required. The present study was designed to address the methodological shortcomings in previous research and describes the investigation of measures of frequency, severity and duration for both panic and limited symptom attacks each separately and combined as total measures rated by a self-report prospective event sampling method employed within a large controlled treatment outcome study. Panic measures were collected pre, mid and post treatment. Patients in the present study received treatment for panic disorder and agoraphobia by fluvoxamine, placebo, fluvoxamine + cognitive behaviour therapy (CBT), placebo + CBT, or CBT alone.

6.2 Method

6.2.1 Subjects

Patients in the present study were those treated in the main study (Sharp et al 1996), reported here as Chapter 4. Patients were referred by general practitioners (GP) and were those considered suitable for pharmacological and/or psychological treatment. All

patients were seen for all appointments in their local GP clinic. Following initial GP assessment and referral all patients were seen by a clinical psychologist for semi-structured interview to ascertain patient characteristics, presenting condition, and severity of illness.

6.2.2. Inclusion criteria

Inclusion criteria were those employed in the main treatment outcome study and are reproduced in detail elsewhere (Sharp et al 1996, Chapter 4). Main inclusion criteria were: panic disorder with or without agoraphobia conforming to Diagnostic and Statistical Manual of Mental Disorders Third Edition - Revised (DSMIII-R, 1987) criteria; a minimum score of 15 on the Hamilton Anxiety Scale (Hamilton 1959); a maximum score of 20 on the Montgomery Asberg Depression Rating Scale (Montgomery & Asberg 1979); symptoms which had lasted three months or longer; no psychotropic medication in the 28 days prior to entry and throughout the study treatment period; aged between 18 and 70 years inclusive.

Over three years 238 patients were referred by GPs, of these 193 entered the study. Analysis was conducted on a sample of 149 completers and defined completers. Patients were randomly allocated to one of five treatment groups; fluvoxamine (FL) (n = 29), placebo (PL) (n = 28), fluvoxamine plus cognitive behaviour therapy (FL+CBT) (n = 29), placebo plus cognitive behaviour therapy (PL+CBT) (n = 33), and cognitive behaviour therapy (CBT) (n = 30). Demographic details of the sample have been given in detail previously (Sharp et al 1996, Chapter 4).

6.2.3.Treatments

All patients were seen to an identical schedule of contact and received either fluvoxamine, placebo, fluvoxamine plus cognitive behaviour therapy (CBT), placebo plus CBT, or CBT alone. Treatment specifications and schedules of contact were those of the main study and are described in more detail elsewhere (Sharp et al 1996, 1997b, Chapter 4).

6.2.4. Procedure

Following assessment and referral by their GP, patients were seen by the psychologist therapist for initial assessment (Day -7) when they were randomised to treatment groups. Over the 13 week treatment period all patients received treatment to an identical schedule of contact with treatment appointments at Day -7, 0, 7, 14, 28, 42, 56, 70 and 84. Pre, mid and post treatment assessments were conducted at days -7, 42, and 84 respectively. Patients were also seen for follow-up at 6 months. Individual appointments lasted a minimum of 30 and a maximum of 60 minutes with all groups receiving an approximately equivalent amount of therapist contact.

6.2.5 Measures

Panic attacks and limited symptom attacks were measured using a prospective self-report event-sampling method. Patients were given a panic diary in which they were to record any panic attacks, if possible, immediately after they occurred, and certainly on the same day as they occurred. Thus retrospective reporting bias was minimised. For each attack patients were required to rate, the severity of the attack on a scale ranging from 0 - "not at all severe" to 10 - "extreme the worst it could be", and the duration of the attack in minutes. The rating form also listed the 13 DSM III-R panic symptoms and patients were required to mark each symptom felt during the attack. Copies of the panic diary are given in Appendix II. Patients were not informed of the number of symptoms required for the attack to be classified as either a full panic attack (4 symptoms or more), or a limited symptom attack (3 symptoms or less). Thus patients record of number of symptoms endorsed would not be influenced by any prior definition of panic attacks. Definition of attacks as either panic or limited symptom attacks was carried out by the therapist after data collection. As in previous studies (Telch et al 1993, De Beurs et al 1993, De Beurs et al 1995), panic diaries were completed by patients in the present study for one week recording periods prior to Day 0, Day 42, and Day 84. Measures of frequency, mean severity, and mean duration were derived for each treatment group for panic attacks and limited symptom attacks both separately and combined as total attacks (panic attacks plus limited symptom attacks) for each assessment point (Day 0, Day 42,

and Day 84). As some doubt has been expressed regarding patient compliance with panic diary procedures (Shear & Maser 1994), and given the procedural complexities and lack of monitoring possible for longer term recording periods, patients were not requested to complete panic attack diaries during the follow-up phase of the treatment outcome study. Patients who attended the six month follow-up assessment were however asked if they had experienced any panic attacks during the follow-up period and a "yes" or "no" answer recorded.

6.3 Results

6.3.1.Statistical Analysis

As one of the main intentions of the study was to investigate panic measures as treatment outcome variables the sample included data only from those patients who had experienced panic attacks and/or limited symptom attacks during the week prior to the first assessment point (Day 0). In this way meaningful changes during treatment could be assessed and the difficulties in interpreting apparent increases in panic found during treatment for patients scoring zero at initial assessment in some previous studies (De Beurs et al 1993) avoided. The numbers of subjects in each treatment group for the purposes of the present study were FL = 22, PL = 24, FL+CBT = 27, PL+CBT = 28, and CBT = 27. Potential differences between groups in panic variables were assessed by means of repeated measures analysis of variance with a between subjects factor, treatment group, and a within subjects factor, assessment point. Significant results were further investigated for each assessment point using simple effects one-way analysis of variance with *post hoc* Scheffe tests of significance. Within group changes over treatment were further tested using paired two-tailed t-tests on pre vs. post-treatment scores.

Initial inspection of the data revealed that most measures showed distributions that were highly positively skewed. In accordance with Ferguson & Cox (1993), any measure which showed a positive skew greater than 1.0 was deemed to require transformation. Distributions for total mean severity, panic mean severity, and limited symptom attack

mean severity, were within acceptable limits and analyses were performed on untransformed data for these variables at all assessment points (Days 0, 42 & 84). Distributions for other measures showed positive skews which varied from 1.76 to 6.02 and therefor required transformed to approximate a more normal distribution and reduce the risk of type I error in analyses. Logarithmic transformations (Log10 (variable + 1)), were employed. Transformations were performed on total frequency, panic frequency, limited symptom attack frequency, total mean duration, panic mean duration, and limited symptom attack mean duration at all three assessment points (Days 0, 42, & 84). For these six variables analyses were performed on transformed data. Means and standard deviations for all variables are reported as original untransformed values. Panic attacks were compared with limited symptom attacks on the variables of frequency, mean severity, and mean duration at each assessment point (Days 0, 42, & 84) using two-tailed paired t-tests. These comparisons were made within subjects and thus included data only for those subjects who recorded both panic attacks and limited symptom attacks at each assessment point.

Results will be presented for (a) total attacks variables (total attacks frequency, total attacks mean severity, total attacks mean duration), followed by (b) panic attack variables (panic attack frequency, panic attack mean severity, panic attack mean duration) and finally (c) limited symptom attack variables (limited symptom attack frequency, limited symptom attack mean severity, limited symptom attack mean duration).

6.3.2. Total attacks frequency, mean severity, and mean duration.

One-way ANOVAs, t-tests, means and standard deviations for total attacks frequency, mean severity, and mean duration are presented in Table 6.1.

Analysis of variance for total attacks frequency revealed significant group ($F(4,122) = 2.23$, $p < 0.05$), and time ($F(2,244) = 85.89$, $p < 0.0001$) effects, but a non-significant interaction term ($F_{(8,244)} = 1.38$, n.s.). Further analysis revealed a significant difference between groups at Day 0 ($F(4,124) = 2.53$, $p < 0.05$), but this difference did not achieve

significance on the *post hoc* Scheffe tests of significance. No other significant differences between groups were found at any other assessment point.

Table 6.1. One-way ANOVAs, t-tests, and means (s.d.) for total attacks frequency, total attacks mean severity, and total attacks mean duration for all groups at each assessment point.

	FL	PL	FL+CBT	PL+CBT	CBT	F
Total Attacks Frequency						
Day 0	5.27	4.25	4.81	5.86	7.71	2.53*
	(3.76)	(3.87)	(4.39)	(5.22)	(5.07)	
Day 42	3.23	3.13	1.81	2.41	4.81	2.15
	(3.69)	(4.12)	(2.37)	(3.28)	(4.52)	n.s.
Day 84	2.18	2.63	1.63	1.03	3.37	2.03
	(3.36)	(3.89)	(2.83)	(1.99)	(5.04)	n.s.
t	4.28****	4.11****	6.50****	6.88****	4.73****	
Total Attacks Mean Severity						
Day 0	4.05	3.70	3.46	3.66	4.13	0.60
	(1.97)	(1.89)	(1.93)	(1.78)	(1.72)	n.s.
Day 42	2.93	2.88	1.39	2.25	3.41	2.72*
	(2.49)	(2.54)	(1.93)	(2.28)	(2.75)	
Day 84	2.02	2.34	0.74	1.28	2.20	2.42
	(2.72)	(2.61)	(1.29)	(2.35)	(2.40)	n.s.
t	3.04**	2.30*	6.19****	5.58****	3.45**	
Total Attacks Mean Duration						
Day 0	48.40	59.57	38.48	50.32	52.04	0.44
	(69.80)	(70.38)	(44.54)	(73.01)	(54.51)	n.s.
Day 42	29.11	55.90	29.61	51.54	30.00	1.03
	(41.03)	(66.86)	(64.21)	(75.38)	(35.71)	n.s.
Day 84	35.78	55.31	11.0	12.84	23.27	1.55
	(76.79)	(107.38)	(22.73)	(33.47)	(37.46)	n.s.
t	3.79***	2.41*	6.11****	5.18****	4.58****	

* $p < 0.05$, ** $p < 0.01$ *** $p < 0.001$, **** $p < 0.0001$, n.s. not significant

t-test refer to pre (Day 0) vs. post (Day 84) comparisons

Within group analyses revealed significant reductions in total frequency for all groups (all $p < 0.0001$). Thus the frequency of panic attacks and limited symptom attacks combined reduced significantly during treatment for all treatment groups with there being no significant differences between groups at any point during treatment.

Analysis of variance for total attacks mean severity revealed significant group ($F(4,119) = 2.76$, $p < 0.05$), and time ($F(2,238) = 45.79$, $p < 0.0001$) effects, but no significant interaction term ($F(8,238) = 0.88$, n.s.). Further analysis revealed a significant difference between groups at Day 42 only ($F(4,120) = 2.72$, $p < 0.05$) although between group differences were not sufficient to achieve significance on *post hoc* Scheffe tests. All groups showed significant within group pre-post treatment improvement with the active treatment groups (FL, FL+CBT, PL+CBT, CBT) showing a stronger response (all $p < 0.001$ and above) than the PL group ($p < 0.05$).

Analysis of variance for total attacks mean duration revealed a significant finding for time ($F(2,202) = 52.35$, $p < 0.0001$) only, with neither the group ($F(4,101) = 1.46$, n.s.) nor the interaction ($F(8,202) = 0.86$, n.s.) terms reaching significance. Within group t-tests showed significant improvement (all $p < 0.001$ and above) for the active treatment groups (FL, PL, FL+CBT, PL+CBT, CBT). Pre-post analysis was also significant for the PL group although at a lower level of significance, ($p < 0.05$).

The overall pattern of results for the measures of total attacks frequency, mean severity, and mean duration, was of one of significant, and equivalent improvement in these measures across all groups throughout treatment.

6.3.3. Panic attack frequency, mean severity, and mean duration.

One-way ANOVAs, t-tests, means and standard deviations for panic attack frequency, mean severity, and mean duration are presented in Table 6.2.

Analysis of variance for panic attack frequency revealed a significant effect for time only ($F(2,156) = 55.90$, $p < 0.0001$) only, with neither the group ($F(4,78) = 0.48$, n.s.), nor the interaction ($F(8,156) = 0.55$, n.s.) terms reaching significance. Thus all groups showed significant change over treatment, there being no significant differences between

groups at any assessment point. All groups showed significant pre-post treatment changes in panic frequency (all $p < 0.01$ and above).

Table 6.2. One-way ANOVAs, t-tests, and means (s.d.) for panic attack frequency, mean severity, and mean duration, for all groups at each assessment point.

	FL	PL	FL+CBT	PL+CBT	CBT	F
Panic attack frequency						
Day 0	4.19	3.57	4.00	4.26	4.50	0.26
	(3.19)	(3.72)	(3.66)	(3.16)	(4.15)	n.s.
Day 42	2.13	2.64	1.20	1.84	2.26	0.69
	(2.60)	(3.81)	(2.11)	(1.80)	(2.77)	n.s.
Day 84	1.56	2.00	0.73	1.21	1.30	0.44
	(2.83)	(3.46)	(1.62)	(2.18)	(2.49)	n.s.
t	3.72***	4.78****	5.93****	4.51****	4.43****	
Panic attack mean severity						
Day 0	5.12	4.86	4.14	4.65	6.15	2.45
	(1.95)	(1.47)	(1.97)	(2.15)	(2.05)	n.s.
Day 42	3.45	2.58	1.03	2.43	2.84	1.64
	(2.66)	(2.91)	(1.99)	(2.45)	(3.27)	n.s.
Day 84	2.41	2.52	0.66	1.81	1.12	2.21
	(2.85)	(3.31)	(1.41)	(2.75)	(2.19)	n.s.
t	4.10***	3.55***	7.44****	5.90****	6.70****	
Panic attack mean duration						
Day 0	38.93	96.08	56.14	68.72	63.68	0.45
	(29.04)	(93.38)	(54.13)	(93.21)	(77.92)	n.s.
Day 42	34.15	68.27	3.62	47.36	20.35	2.07
	(43.75)	(80.21)	(6.44)	(73.82)	(35.09)	n.s.
Day 84	34.92	41.18	2.46	10.69	15.79	1.13
	(71.14)	(76.59)	(6.42)	(21.11)	(44.82)	n.s.
t	2.86***	3.41***	7.29****	4.57****	5.65****	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, n.s. not significant.
t-test refer to pre (Day 0) vs. post (Day 84) comparisons

Analysis of variance for panic attacks mean severity revealed an identical pattern to that for panic attack frequency with a significant finding for time only ($F(2,154) = 58.00$, $p < 0.0001$), with the group ($F(4,72) = 2.12$, n.s.) and interaction ($F(8,154) = 1.39$, n.s.) terms failing to reach significance. This again indicates improvement over treatment that is equivalent across groups. Within group analysis also showed significant improvement in panic attack severity for all groups ($p < 0.01$ and above).

Analysis of variance for panic attack mean duration showed yet again the same pattern with a significant finding for time ($F(2,122) = 56.34$, $p < 0.0001$) only. The group ($F(4,61) = 1.53$, n.s.) and interaction ($F(8,122) = 1.03$, n.s.) terms again failed to reach significance. Within groups analysis again showed a significant reduction in panic attack duration across treatment for all groups ($p < 0.01$ and above). Thus for panic attack measures the same consistent pattern emerged once more indicating significant improvement over time with no significant differences between groups at any point.

6.3.4. Limited symptom attack frequency, mean severity, and mean duration

One-way ANOVAs, t-tests, means and standard deviations for limited symptom attack frequency, means severity, and mean duration are presented in Table 6.3.

Analysis of variance for limited symptom attack frequency revealed a significant effect for group ($F(4,99) = 2.48$, $p < 0.05$), and time ($F(2,198) = 75.99$, $p < 0.0001$), but an insignificant interaction term ($F(8,198) = 1.20$, n.s.). Further analysis showed a significant difference between groups at day 84 ($F(4,99) = 2.79$, $p < 0.05$) only with *post hoc* Scheffe tests indicating a difference between the PL+CBT and CBT groups ($p < 0.05$). Within groups analysis revealed a significant reduction in limited symptom attack frequency across treatment for all groups ($p < 0.01$ and above).

Analysis of variance for limited symptom attack mean severity revealed a significant effect for group ($F(4,94) = 2.98$, $p < 0.05$) and for time ($F(2,188) = 77.23$, $p < 0.0001$) but not for the interaction term ($F(8,188) = 1.49$, n.s.). Further analysis indicated a significant difference between groups at Day 84 only ($F(4,94) = 3.01$, $p < 0.05$) with *post hoc* Scheffe test indicating a significant difference between the PL+CBT and CBT

groups ($p < 0.05$). Within group analysis revealed a significant reduction in limited symptom attack frequency across treatment for all groups ($p < 0.001$ and above).

Table 6.3. One-way ANOVAs, t-tests, and means (s.d.) for limited symptom attack frequency, mean severity, and mean duration, for all groups at each assessment point.

	FL	PL	FL+CBT	PL+CBT	CBT	F
Limited symptom attack frequency						
Day 0	2.72	3.25	2.92	3.87	4.92	1.57
	(1.71)	(3.55)	(2.21)	(3.68)	(3.92)	n.s.
Day 42	1.83	2.06	1.13	2.26	2.92	1.74
	(2.53)	(2.65)	(1.48)	(2.51)	(3.71)	n.s.
Day 84	1.11	1.75	1.25	0.27	2.80	2.79*
	(1.99)	(3.84)	(2.42)	(0.94)	(4.23)	
t	4.31****	3.70***	5.22****	9.10****	3.95***	
Limited symptom attack mean severity						
Day 0	3.26	2.73	2.82	3.02	3.11	0.31
	(1.84)	(1.41)	(1.87)	(1.59)	(1.42)	n.s.
Day 42	1.20	1.93	1.03	1.14	2.58	2.28
	(1.44)	(2.23)	(1.63)	(1.69)	(2.45)	n.s.
Day 84	1.35	1.31	0.47	0.22	1.86	3.01*
	(2.44)	(2.03)	(0.98)	(0.69)	(2.36)	
t	3.83***	4.07***	7.53****	11.90****	3.78***	
Limited symptom attack mean duration						
Day 0	53.0	57.57	32.09	23.85	45.65	0.78
	(79.29)	(101.23)	(36.64)	(23.87)	(41.85)	n.s.
Day 42	17.26	36.43	23.55	30.21	28.22	2.27
	(31.27)	(53.06)	(59.41)	(61.65)	(36.80)	n.s.
Day 84	22.26	37.46	11.24	9.47	22.41	1.58
	(48.81)	(78.61)	(24.15)	(34.72)	(34.65)	n.s.
t	4.48****	3.16***	5.89****	5.18****	3.57***	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, n.s. not significant.

t-test refer to pre (Day 0) vs. post (Day 84) comparisons

Analysis of variance for limited symptom attack mean duration revealed a pattern identical to that found with panic attack data with a significant effect for time only ($F(2,170) = 130.25$, $p < 0.0001$). Results for group ($F(4,85) = 1.86$, n.s.) and the interaction term ($F(8,170) = 0.76$, n.s.) did not reach significance. This pattern is indicative of significant change across treatment with there being no significant differences between groups at any point. Within group analysis supported this finding with all groups showing a significant reduction in limited symptom attack mean duration pre-post (all $p < 0.01$ and above).

6.3.5. Follow-up data

Table 6.4 gives the information on panic attacks given at 6 month follow-up. Patients were asked at 6 month follow-up if they had experienced any panic attacks during the follow-up period.

Table 6.4. Number (%) of patients in each group attending follow-up, receiving post study treatment and suffering continued panic attacks over follow-up period.

	FL n = 29	PL n = 28	FL+CBT n = 29	PL+CBT n = 33	CBT n = 30
No (%) of Ss free of major panic attacks at Day 84	20 (68.9)	17 (60.7)	24 (82.7)	25 (75.7)	21 (70.0)
No of attenders at 6 Month follow up	23 (79.3)	21 (75.0)	24 (82.8)	30 (90.9)	28 (93.3)
No of attenders at 6 Month follow up with no subsequent treatment	12 (41.4)	8 (28.6)	18 (62.1)	20 (60.6)	15 (50.0)
No of attenders at 6 Month follow up with no subsequent treatment and no panic attacks	6 (20.7)	4 (14.3)	11 (37.9)	13 (39.3)	10 (33.3)

This data was collected using a retrospective procedure, which furthermore does not differentiate between panic, and limited symptom attacks, these findings must therefor be treated with some caution. The criteria for post study treatment were exactly those employed in the main study and are detailed elsewhere (Sharp et al 1996, Chapter 4).

The table indicates a fall off in the number of patients remaining panic free during the follow-up period as compared with patients panic free at Day 84. This fall off is less marked in those patients who received CBT (FL+CBT, PL+CBT, CBT). This pattern of apparent superiority for patients receiving CBT was also found for other follow-up data in the main study (Sharp et al 1996, Chapter 4).

6.3.6. Panic attacks vs. Limited symptom attacks

A comparison of panic attacks and limited symptom attacks was made for each variable (frequency, mean severity, and mean duration) at each assessment point (Day 0, Day 42, and Day 84). Comparisons were made using two-tailed t-tests for related samples. Data were compared only for subjects who had experienced both panic attacks and limited symptom attacks at a given assessment point and was thus a within subjects analysis. Results are given in Table 6.5, and are expressed as t-scores. A clear pattern emerges from Table 6.5, panic attacks did not differ significantly from limited symptom attacks in terms of frequency at any assessment point, and differed significantly in terms of mean duration at Day 0 only where panic attacks showed a significantly longer mean duration. Panic attacks did differ significantly and consistently from limited symptom attacks in terms of mean severity with panic attacks being rated as significantly more severe at Day 0, Day 42, and Day 84.

Table 6.5 Comparison of panic attacks with limited symptom attacks on frequency, mean severity and mean duration at each assessment point using t-test for related samples.

	Frequency	Mean severity	Mean duration
DAY 0	$t = 1.11$, $df = 59$	$t = 10.61$, $df = 58$	$t = 3.35$, $df = 51$
	n.s.	$p < 0.0001$	$p < 0.01$
DAY 42	$t = 0.83$, $df = 34$	$t = 3.66$, $df = 34$	$t = 0.26$, $df = 28$
	n.s.	$p < 0.001$	n.s.
DAY 84	$t = 1.94$, $df = 20$	$t = 3.51$, $df = 20$	$t = 0.26$, $df = 17$
	n.s.	$p < 0.01$	n.s.

6.4 Discussion

The current study set out to investigate the use of panic attack variables as treatment outcome measures and in so doing to improve on the methodology of previous studies. In the current study panic attacks were rated prospectively using a self-report event recording method. Patients recorded the severity and duration of any attacks as well as their frequency. Patients were not briefed on the distinction between panic attacks and limited symptom attacks in terms of number of symptoms thus permitting a *post hoc* comparison of panic attacks with limited symptom attacks in terms of frequency severity and duration. This comparison was made within subjects.

The overall impression gained from the treatment outcome results of the present study is that all variables showed significant improvements pre-post over treatment with there being very few instances of differences between groups. This is in accord with the previous studies reviewed, where only four of the 12 studies discussed (Ost 1988, Telch et al 1993, De Beurs et al 1995, Oehrberg et al 1995) actually found panic variables to differentiate between competing treatments. In the present study, for total variables, possible between group differences on total frequency at Day 0, and total mean severity at Day 42, indicated on one-way analyses of variance failed to reach significance on the post hoc Scheffe test, an admittedly conservative criterion. Panic attack variables showed a consistent pattern across all variables and assessment points. All five treatment groups showed significant improvement over treatment with there being no differences between treatment groups on any variable at any assessment point. The only significant between group differences were found for the limited symptom attack variables where at Day 84, the CBT group showed a greater frequency and greater severity of limited symptom attacks than the PL+CBT group. There were no other significant between group differences in the limited symptom attack variables. This pattern of findings is relevant to a consideration of the utility of panic attack variables as indices of between group differences in comparative treatment outcome studies. The measures of panic attack and limited symptom attack frequency, severity, and duration employed in this study all showed change over treatment with all groups showing statistically significant improvement pre to post-treatment. The measures did not discriminate between groups

in strength or speed of response and as such may not be particularly informative discriminatory variables in treatment outcome research. This is perhaps surprising given that other measures of therapist and patient rated anxiety, depression, and avoidance employed with this patient group (Sharp et al 1996, Chapter 4) did show some differences between treatment groups in strength and consistency of response. An inspection of the group means for the panic attack variables in this study might suggest the existence of significant between group differences particularly at treatment end point, Day 84, however these failed to reach statistical significance. The relatively large standard deviations found for most variables suggest that panic attack variables are rather volatile. This point has indeed been noted by other researchers (Basoglu et al 1992). Furthermore, in accord with previous suggestions (Barlow 1988), panic attack variables would appear to be a rather lenient way of assessing treatment outcome, showing significant change over treatment even for the PL treatment group, and as such are therefor of limited utility as discriminating treatment outcome variables. In the present study, panic attacks improved as much in a group receiving placebo medication and balanced therapist contact (PL) as in the other groups receiving targeted active anti-panic treatments (FL, FL+CBT, PL+CBT, CBT). This is an important finding as the present study is the first to investigate panic attack variables within a design that includes a therapist contact control condition (PL). In studies reviewed above, those that have included control conditions have used no treatment waiting-list controls. The novel finding of a strong treatment response in terms of panic attack variables found here for the PL group which included a therapist contact control is therefor significant. This finding suggests that caution should be exercised in interpreting studies which claim support for specific anti-panic properties of treatments if these are based on study designs which measure panic attacks but do not include a control for therapist contact or do not show panic attack results for the active treatments to be significantly superior to those for therapist contact controls, as such positive findings may simply be due to non-specific elements of treatment. Some potential differences between groups did appear in the follow-up analysis where patients in the groups receiving CBT (FL+CBT, PL+CBT, CBT), showed a greater preservation of panic free status at 6 month follow-up than did

those patients receiving medication alone (FL, PL). This pattern is identical to that found for preservation of clinical significance of outcome found for patient and therapist rated measures of anxiety and avoidance reported elsewhere (Sharp et al 1996, Chapter 4). Some caution must be exercised in interpreting these follow-up findings. The continuous prospective event recording method of measuring panic variables during the treatment phase of the study was not continued over the follow-up period. Thus panic attacks were assessed retrospectively at follow-up and the accuracy and validity of this method can be questioned. It is nonetheless noteworthy that this less reliable retrospective method did produce a pattern of results in keeping with other assessment measures.

The analysis comparing panic attacks with limited symptom attacks at each assessment point yielded results in keeping with the only other study to date to compare panic attacks with limited symptom attacks within patients (Krystal et al 1991). The Krystal et al (1991) study and the present study found that patients rated full panic attacks as more severe than limited symptom attacks and furthermore the present study found that this difference in severity persisted throughout treatment across all three assessment points. The present study also found a significant difference between panic attacks and limited symptom attacks in duration as had a previous study (De Beurs et al 1994) with panic attacks being of longer duration. This difference existed at pre-treatment assessment (Day 0) only and disappeared once treatments had been initiated. The present study is the first investigation to compare panic attacks with limited symptom attacks throughout a program of treatment. It should be borne in mind, however, that the validity of the *post hoc* distinction of panic attacks from limited symptom attacks employed in the present study does rely on the accuracy and consistency of patients reporting of number of symptoms experienced during any given attack. Given the evidence from the present study already discussed on the universal effect of all treatment interventions in reducing scores on all panic attack and limited symptom attack variables, the persistence of the panic vs. limited symptom attack difference on severity throughout the treatment period is noteworthy, testifying to the robustness of this difference.

The present study did not require patients to distinguish between spontaneous and situational panic attacks. Some valuable discriminatory data may have been lost as a result although this is unlikely given the weight of evidence suggesting the equivalence of these two forms of panic (Margraf et al 1987, Street et al 1989, Krystal et al 1991, Basoglu et al 1992). The necessary conclusion from the current study is that the employment, in treatment outcome studies, of more detailed panic attack variables including measures of panic attack and limited symptom attack severity and duration such as those employed here, is unlikely to yield much in the way of useful data. In the present study, panic attacks improved significantly and equally regardless of intervention employed. The follow-up results do however suggest that the occurrence of panic attacks during post treatment follow-up may be a more promising subject of study, and may reveal differential rates of recurrence of panic attacks during follow-up. It is regrettable that in the present study, patients were not required to continue completing the panic diaries over the follow-up period. This methodology is required to reinforce the tentative follow-up results of the present study. The comparison of limited symptom and full-blown panic attacks suggests that limited symptom attacks can be regarded as less severe versions of the full panic attacks, however, this difference does not in itself justify the exclusion of limited symptom attacks from treatment outcome analysis as has been done in many previous studies. As a final point, replication of the present study is required, firstly as some aspects of the study design are novel, and secondly to further investigate the seemingly counterintuitive conclusion that panic attack variables appear to rather uninformative treatment outcome measures when applied to treatments for panic disorder and agoraphobia. The present study has been reported elsewhere as Sharp & Power (Submitted)(b).

CHAPTER 7 AN INVESTIGATION OF PROGNOSTIC INDICATORS OF TREATMENT OUTCOME

7.1 Introduction

Treatment outcome studies have as their principal goal the identification and measurement of treatment responses both within and between treatments. It has long been the ambition of clinicians to further supplement findings of treatment efficacy by identifying pre-treatment or early treatment variables which might act as predictors of final post-treatment response. Armed with such information the clinician might be more able to fine-tune treatments according to the requirements of each patient. Knowing at the outset of treatment which patients were likely to respond and which were more liable to require, for example, additional support would be of great advantage to the clinician. The assumption that responses to pre-treatment measures may predict longer term outcome is derived from early investigations with patients suffering from schizophrenia (e.g. Wing 1973, Strauss & Carpenter 1974). Given the clinical prevalence of panic disorder with and without agoraphobia it is not surprising that an interest in possible prognostic indicators has also developed in this area. The relatively few studies that have been conducted with patients suffering from panic disorder and agoraphobia have usually employed exposure based treatments and have often produced equivocal findings. The overall picture of few remarkable or consistent findings is an often mentioned feature of this research (Thomas-Peter et al 1983, Jansson et al 1987, Keijsers et al 1994). Methodological problems exist with previous research that might account for the disappointing results obtained thus far. Problems such as differences between studies in the measurement of prognostic variables and in the definition of treatment outcome, and small sample sizes employed to support too many variables leading to sample-bound nonreplicable findings, have been noted (Chambless & Gracely 1988, Keijsers et al 1994). Other problems exist with basic study design. These will be discussed first. Some studies (Emmelkamp & Van Der Hout 1983, Cox et al 1988, Fischer et al 1988), have employed simple between group designs where patients were defined as successes or failures according to criteria applied to post-treatment response. Among such studies these two groupings of patients have been compared on mean scores for a variety of pre-treatment measures using between group statistics. The assumption underpinning this procedure is that having differentiated two groups of

patients according to post-treatment variables, any subsequent between group differences on pre-treatment variables will be related meaningfully to the post-treatment differentiation. Without further empirical justification this assumption cannot be accepted unconditionally. The studies which have employed this methodology have found between group differences on pre-treatment variables such as, marital satisfaction, quality of therapeutic relationship, and perceived parental characteristics (Emmelkamp & Van Der Hout 1983), and the psychoticism and positive symptom index subscales of the Hopkins Symptom Checklist-90 (Cox et al 1988). The existence of these between group differences in pre-treatment variables has undoubtedly been established, given the study designs, however, their power and validity as predictors of post-treatment response has not. A method of analysis is required whereby the relationship between pre, and post treatment variables can be assessed. A simple form of such an analysis would be the use of multiple bi-variate correlations calculated between pairings of pre and post treatment variables. One study used such a method (Thomas-Peter et al 1983), conducting 46 individual bi-variate correlations (Pearson's $\underline{r}$) on a sample size of $n = 17$.Given that only three significant correlations were found (all at $p < 0.05$) and no correction for multiple testing was employed, the results of this study must be treated with caution. The study clearly illustrates the problems inherent in simple correlational analyses. More sophisticated and potentially more controlled analyses are possible using multivariate techniques such as multiple regression analysis. This technique has been favoured in more recent studies. Three studies have employed regression analyses in an attempt to assess the viability of a number of potential prognostic variables. The first of these (Chambless & Gracely 1988), investigated treatment response as measured by the Avoidance Alone scale of the Mobility Inventory (Chambless et al 1985) in a sample of $n = 134$ patients with DSM III agoraphobia with panic attacks who were treated with an intensive exposure-based treatment programme. The relationship between post treatment scores on this single dependant variable and a range of intervening variables was investigated using a series of regression analyses with each predictor being analysed in a separate regression. Predictors employed included demographic information, and measures of assertion, agoraphobic avoidance, anxiety based body sensations,

depression, trait anxiety, social avoidance, and marital satisfaction. Only two variables were found to be significant predictors of treatment end-point agoraphobia avoidance scores, these were anxiety based body sensations, and marital dissatisfaction with the latter variable appearing to operate as a suppressor variable. There are some problems with this study, some specific to the individual study design, others more general to the type of analysis. The more general points will be discussed later. Regarding the problems specific to this study design, by employing a series of separate and individual regression analyses Chambless & Gracely (1988) did not allow any control for the potential intercorrelation of their chosen predictor variables. Given that these included measures of, for example, trait anxiety, social avoidance, and anxiety based bodily sensations, some degree of intercorrelation is likely. This makes the few significant findings in this study difficult to interpret. The second study (Jansson et al 1987) differed from the Chambless & Gracely (1988) study in employing four dependant variables all of which were derived from a behavioural test walk. Patients were required to attempt a hierarchy of 15 agoraphobic situations and the percentage of situations completed recorded. Measures of subjective anxiety (on a 0-10 scale), and heart rate were also taken during the test walk. These three measures along with a composite measure of the change scores on each constituted the dependant variables for this study. Scores on the dependant variables were available for treatment end-point and 7 and 15 month follow-up. A total of n = 33 patients with agoraphobia received an equal number of sessions of either exposure in vivo or applied relaxation. Potential intervening variables in this study were, demographic variables, patient's treatment expectancies, depression, agoraphobic avoidance, autonomic perception, panic attack variables, and marital relationship. Each of these intervening variables was entered stepwise into a multiple regression for each dependent variable at each assessment point (treatment end-point, 7 and 15 month follow-up). Again few significant predictors were found. Outcome immediately after treatment was predicted by age and self-rated anxiety during the behavioural test walk. Outcome at follow-up was predicted again by self-rating of anxiety, and initial behaviour scores and initial heart rate scores from the first behavioural test walk. The authors concluded that only directly phobia-related measures such as self-rated anxiety, and

heart rate were good predictors of outcome. This of course may reflect no more than the fact that the chosen dependant variables for this study were all derived from a directly phobia related behavioural test walk. The study is however noteworthy as an attempt to employ a more comprehensive assessment and analysis strategy than previous investigations, although the sample size (n = 33) was small relative to the number of intervening variables used thus results may represent an over-prediction. A more serious problem with the study concerns the follow-up findings. No mention is made of post study treatment received during the follow-up phase of the study. Patients were followed up to 15 months post treatment thus there was considerable opportunity for such treatment to occur. As post study treatment was not reported in this study it's influence on both outcome results and on subsequent regression analyses cannot be estimated. This is a potentially serious flaw. The third study to employ a regression analysis (Keijsers et al 1994) investigated treatment outcome indexed by agoraphobic avoidance and frequency of panic attacks, measured using the Mobility Inventory (Chambless et al 1985), and frequency of physical panic symptoms measured using a non-standardised self-report scale. Predictor variables included catastrophic agoraphobic cognitions, levels of depression and general anxiety, quality of therapeutic relationship, patient motivation for treatment, personality psychopathology, and marital dissatisfaction. A sample of n = 60 DSM III-R panic disorder with agoraphobia patients were treated with a 12 session standardised exposure-based behavioural treatment programme. Linear regression analyses on each of the outcome variables revealed a small number of significant predictor variables. Catastrophic agoraphobic cognitions correlated significantly with all three outcome variables, as did patients motivation for treatment. Level of depression correlated significantly with frequency of panic attacks, and personality psychopathology with agoraphobic avoidance. After applying a correction for multiple testing (Bonferroni correction) only catastrophic agoraphobic cognitions remained as a significant predictor variable. This study (Keijsers et al 1994) used a more controlled assessment and analysis strategy and employed a larger sample size than previous studies (e.g. Jansson et al 1987), and findings can be regarded as more robust as a result. The Keijsers et al (1994) nonetheless suffers from a significant problem common to all the studies employing

regression methodology, that is, whilst regression techniques are suitable for identifying any relationship between outcome variables and predictor variables they can give no indication of whether these relationships have any real clinical relevance. Predictor variables are regressed onto outcome variables with the latter operating usually as continuous variables. Whilst an outcome variable may show statistically significant change following treatment such change may not be of sufficient magnitude to constitute a genuinely clinically significant improvement. Methods have been developed to establish standardised criteria of clinically significant change (Jacobson & Ravenstorf 1988, Jacobson & Truax 1991), and these are now being recommended for use in treatment outcome studies (Shear & Maser 1994). Unfortunately regression techniques which employ continuous outcome variables do not permit the investigation of the clinical significance of change over treatment. This is unfortunate, as it is the prediction of clinically significant change, rather than change of lesser magnitude, which is of principal interest to the clinician.

This problem has been recognised by some researchers who have attempted further analyses over and above the standard regression techniques. These attempts usually involve dichotomising the sample as treatment successes or failures and attempting to predict group membership using the predictor variables employed in their regression analyses. Chambless & Gracely (1988) used Jacobson et al's (1984) Reliable Change Index (RCI) to classify their sample as treatment successes or failures according to scores on their outcome measure of agoraphobic avoidance. The RCI formula expresses the reliability of an outcome score as a function of the post-test minus the pre-test score divided by the standard error of the difference scores. If this value is greater than a prior established cut-off point, the change can be regarded as reliable. Caution should be exercised here however, as a change which is reliable may not necessarily be clinically significant. This caveat notwithstanding, Chambless & Gracely (1988) dichotomised their sample using the RCI and investigated their chosen predictor variables using a series of point-biserial correlations. This method suffers from the same problem as the repeated single regression analysis used in this study and criticised above. A series of individual point-biserial correlations do not permit any assessment of potential

intercorrelations amongst predictor variables, thus any significant findings are difficult to interpret. As it happens, Chambless & Gracely (1988) found no significant predictors of treatment success using this methodology. In the only other attempt to investigate the clinical significance of outcome in an investigation of prognostic indicators Keijsers et al (1994) calculated an "improvement percentage index" for each of their three outcome variables. This measure was idiosyncratic to this study and no other investigation of its validity as an index of clinically significant change was reported. The improvement percentage index classified approximately 50% of the sample as treatment failures on their agoraphobic avoidance and physical panic symptoms outcome variables, and 20% were treatment failures on the panic attack frequency outcome variable. Keijsers et al (1994) employed a discriminant function analysis to identify those predictor variables that predicted group membership (success versus failure) on each of the outcome variables. Such an analysis of course makes assumptions as to the quality of distributions of, and nature of the interrelationships amongst, the predictor and outcome variables. For agoraphobic avoidance, treatment successes and failures were significantly discriminated by catastrophic agoraphobic cognitions, therapeutic relationship, and patient's motivation for treatment. For frequency of panic attacks, the significant predictor variables were catastrophic agoraphobic cognitions, level of depression, therapeutic relationship, and patient's motivation for treatment. For the third outcome variable, physical panic symptoms, group membership was significantly predicted by catastrophic agoraphobic cognitions, level of depression, patient's motivation for treatment, and personality psychopathology. Overall 75% of the sample were classified correctly to the success or failure group. These two studies (Chambless & Gracely 1988, Keijsers et al 1994) are the only two attempts to date to include the clinical significance of treatment as a factor in outcome assessments. Unfortunately in both studies the methods of assessing clinical significance chosen were either idiosyncratic (Keijsers et al 1994), or were not directly related to clinical significance (Chambless & Gracely 1988). Established criteria of clinical significance of treatment outcome exist (Jacobson & Truax 1991) which are based on the assumption that patients start a treatment with scores which place them within the distribution of a clinical population, and following a

successful treatment have scores which fall within the distribution for a normal non-clinical population. Several criteria exist for establishing the occurrence of this shift from clinical to non-clinical distributions and could be used as indices of clinically significant change in investigations of potential prognostic indicators. The selection of the dependant or outcome variables on which the assessments of clinically significant change are made is also important. Previous studies have used assessments that tap only one aspect of panic disorder, usually agoraphobic avoidance (Chambless & Gracely 1988), without employing other potential measures of outcome such as general level of anxiety. Other studies have employed non-standardised measures as outcome variables (Thomas-Peter et al 1983), despite early calls for the use of standardised measures as outcome variables in such research (Huxley et al 1979). Care must also be taken to ensure the validity of chosen outcome measures. In one study (Keijsers et al 1994) outcome measures of panic attack frequency and frequency of physical panic symptoms were used, derived from retrospective ratings contained in the Mobility Inventory (Chambless et al 1985). There is now evidence which indicates that retrospective ratings of panic attack variables are often inflated as compared with prospectively assessed panic attack variables (Margraf et al 1987, Rapee et al 1990b, De Beurs et al 1992), and that retrospective ratings are not therefor an accurate reflection of the clinical reality of the disorder. The effect of employing retrospectively rated panic attack variables as either outcome or predictor variables in prognostic research is not known. The use of such variables should therefor be treated with some caution. The methodological rigour of investigations of prognostic indicators of treatment outcome would be improved if outcome measures based on standardised measures were used. The definitions of clinically significant change derived from these measures should also be conducted using replicable, standardised procedures based on reasonable theoretical principles. The clinically significant change criteria developed by Jacobson and colleagues (Jacobson & Ravenstorf 1988, Jacobson & Truax 1991) are suitable for this purpose.

Having discussed the treatment outcome, or dependant, variables in prognostic studies, some comment on the intervening, or predictor, variables is warranted. As Keijsers et al (1994) note, a large range of predictor variables have been investigated,

often with only limited success. Demographic variables, complaint-related variables such as levels of anxiety depression or agoraphobia, psychological variables such as personality psychopathology, and social psychological variables such as marital relationship, have all been investigated as potential predictors of treatment response. The quality and replicability of such measures has varied greatly between studies, and the comments above in relation to outcome variables apply equally well to predictor variables. That is, methodological rigour and study replicability would be enhanced by the use of standardised measures as predictor variables. The construct validity of the measures used as predictor variables is also important. This is well illustrated in the case of measures of personality. All the studies which have assessed personality have included assessments of DSM Axis II personality disorders only. Thus the only facet of personality investigated is personality psychopathology (e.g. Keijsers et al 1994). This is also the case in other studies of the relationship between personality and panic disorder and agoraphobia (Mavissakalian & Hamann 1987, Chambless et al 1992, Tyrer et al 1993). This is a flawed strategy that assumes that only classifiable disorders of personality will have deleterious effects on treatment outcome, and also denies, by implication, that personality can have a positive influence on treatment response. Less clinically focused measures of personality might repay investigation.

The foregoing discussion has suggested that research into possible prognostic indicators of treatment outcome for panic disorder and agoraphobia may provide clinically useful information. Improvements in study methodology including the use of standardised measures of outcome and predictor variables, and the controlled definition of the clinical significance of treatment outcome may increase the value of such research. The present study reports an investigation of prognostic indicators of outcome following treatment for panic disorder with and without agoraphobia using either fluvoxamine, placebo, and cognitive behaviour therapy, each alone and in combination.

7.2 Method

7.2.1. Subjects

Patients in the present study were those who received treatment in the main study (Sharp et al 1996, Chapter 4). Patients were referred by general practitioners (GP) and were those considered suitable for pharmacological and/or psychological treatment. All patients were seen for all appointments in their local GP clinic. Following initial GP assessment and referral all patients were seen by a clinical psychologist for semi-structured interview to ascertain patient characteristics, presenting condition, and severity of illness.

Inclusion criteria were those employed in the main treatment outcome study and are reproduced in detail elsewhere (Sharp et al 1996, Chapter 4). Over three years 238 patients were referred by GPs, of these 193 entered the study. Analysis was conducted on a sample of 149 completers and defined completers. Demographic details of the sample have been given in detail previously (Sharp et al 1996, Chapter 4).

7.2.2.Treatments

All patients were seen to an identical schedule of contact and received either fluvoxamine, placebo, fluvoxamine plus cognitive behaviour therapy (CBT), placebo plus CBT, or CBT alone. Treatment specifications and schedules of contact were those of the main study and are described in more detail elsewhere (Sharp et al 1996, Chapter 4). Following assessment and referral by their GP, patients were seen by the psychologist therapist for initial assessment (Day -7) when they were randomised to treatment groups. Over the 12 week treatment period all patients received treatment to an identical schedule of contact of 9 treatment appointments. Assessments for the present study were conducted pre and post treatment, and at 6 months follow-up.

7.2.3. Measures

7.2.3.1. Outcome Measures

Treatment outcome was assessed on three standardised scales, a therapist report anxiety scale, the Hamilton Anxiety Scale HAM-A (Hamilton 1959), a patient self-report anxiety scale, the Kellner Sheffied Symptom Rating Test SRT (Kellner & Sheffield 1976), and the patient self-report agoraphobia subscale of the Fear Questionnaire FQ-AG (Marks & Mathews 1979). Clinical significance of outcome on these measures was assessed using the criteria proposed by Jacobson and colleagues (Jacobson & Ravenstorf 1988, Jacobson & Truax 1991). These were the measures and procedures used to establish measures of clinically significant improvement in the main study (Sharp et al 1996, Chapter 4). A cut-off score was established for the FQ-AG scores using the data collected on a non-clinical population by Mizes and Crawford (1988). A cut-off score of 8 or below indicated clinically significant change on this measure. Where data on a non-clinical population do not exist, Jacobson and Ravenstorf (1988) recommend a cut-off score for clinically significant change where a patient score falls outside the range of the dysfunctional population by two standard deviations from the pre-treatment mean of that population, in the direction of functionality. This criterion was employed with the other two measures, firstly the HAM-A, where it established a criterion of moderate severity (cut-off score of 12 or below) and secondly, with the SRT, where the variance in this measure gave rise to large standard deviations, and thus a highly stringent criterion of clinically significant change (cut-off score of 5 or below). These cut-off scores for clinically significant change were used to divide the total sample of n = 149 completers into two groups, those achieving clinically significant improvement, and those failing to achieve clinically significant improvement at two assessment points, firstly at treatment end-point, and secondly at 6 month follow-up. At treatment end point (Day 84) the sample was divided into those achieving clinically significant versus non-significant improvement on Day 84 HAM-A, Day 84 SRT, and Day 84 FQ-AG. A fourth division was created, Day 84 treatment responders versus non-responders. To qualify as a treatment responder patients had to achieve the strict criterion of clinically significant change on all three outcome variables. At 6 month follow-up a further criterion was added to the

classification of clinically significant change. It has already been argued (Sharp et al 1996, Chapter 2, Chapter 4), that the occurrence of additional treatment during the follow-up phase confounds follow-up results. In an attempt to avoid this problem, patients who had taken any psychotropic medication, regardless of quantity, or who had attended any appointments with psychologist, psychiatrist, or had any other secondary mental health referral during the follow-up period were deemed to have received follow-up treatment and were excluded from the current analysis. At 6 month follow-up therefor a further four outcome differentiations were available, those without follow-up treatment achieving clinically significant improvement at 6 month follow-up versus all other patients (i.e. those with non-significant improvement at 6 month follow-up and those with significant improvement at 6 month follow-up but additional follow-up treatment) on 6 Month HAM-A, 6 Month SRT, and 6 Month FQ-AG. A fourth division was again created and designated 6 Month Follow-up Responder. To qualify as a 6 Month Follow-up Responder a patient had to achieve clinically significant improvement on all three outcome measures and receive no follow-up treatment. This again constitutes a fairly stringent criterion of follow-up responder.

7.2.3.2. Predictor Measures

Predictor measures were divided into four broad groupings, demographic variables, panic attack variables, complaint-related variables, and personality and social variables. The aim was to attempt as broad a range of measurement as possible without overloading the analysis with a large number of potentially redundant measures. All measures were taken in the week prior to the start of active treatment. The measures in each grouping will be described in turn. Copies of each measure are given in Appendix II.

7.2.3.2.1. Demographic Variables

Patients age and sex were recorded, as was duration of current episode of panic disorder (in months). GP report of previous psychiatric history was also recorded and operationalised as number of previous psychiatric diagnoses given prior to study entry.

7.2.3.2.2. Panic Attack variables

Panic attack variables have been suggested to be a major defining feature of panic disorder. These variables were recorded using a prospective event recording method by patient diary on a weekly basis. A more detailed description of the measurement of panic attack variables and the reasoning behind them is given in Chapter 6. Both panic attacks and limited symptom attacks were measured. In order to reduce the overall number of predictor variables in this study, the scores for panic attacks and limited symptom attacks combined were used i.e. total scores. Pre-treatment scores for total attack frequency, total mean severity, and total mean duration, were used as predictor variables.

7.2.3.2.3. Complaint Related Variables

These variables were included to investigate the influence of aspects of the clinical presentation of panic disorder and agoraphobia on treatment outcome. A measure of therapist rated anxiety was taken using the Hamilton Anxiety Scale HAM-A (Hamilton 1959), and patient self-rated anxiety using the Kellner Sheffield Symptom Rating Test SRT (Kellner & Sheffield 1973). Patients also self-rated agoraphobic avoidance using the agoraphobia subscale of the Fear Questionnaire, FQ-AG (Marks & Mathews 1979). Therapist also rated depression using the Montgomery Asberg Depression Rating Scale MADRS (Montgomery & Asberg 1979). All of these measures were completed at pre-treatment assessment.

7.2.3.2.4. Personality and Social Variables

These measures were included to investigate aspects of patient's personality and social circumstances and their usefulness as predictor variables. Patients completed the Anxiety Sensitivity Index, ASI, (Reiss et al 1986, Peterson & Reiss 1992). This is a 16 item self-report questionnaire that measures fear of, or sensitivity to, anxiety symptoms. Patients respond to questions such as "when I notice that my heart is beating rapidly, I worry that I might have a heart attack" by recording their degree of endorsement of each item on a 5-point Lickert type scale ranging from 0 ("very little"), to 4 ("very much"). Anxiety sensitivity is argued to have a single factor structure (Taylor et al 1992b), and to be conceptually

distinct from trait anxiety (McNally 1989). Patients also completed the Eysenck Personality Questionnaire, EPQ, (Eysenck & Eysenck 1978) from which the Extroversion, E, and Neuroticism, N, scales are reported. In this way two broad dispositional personality traits (E and N), were measured along with a dispositional trait argued to be more specifically related to panic disorder in particular (ASI). Social factors were measured using two scales. Patients completed the Social Maladjustment Questionnaire (SocMal), (Corney & Clare 1985). This is a 33 item self-report questionnaire designed to identify social problems, difficulties, and dissatisfaction. The questionnaire is has 7 sections covering, housing, work, financial situation, social and leisure activities, child/parent and marital relationships, social relationships, and legal problems. Patients endorsed each section that represented an area of difficulty for them, thus a score representing the total number of sections endorsed was recorded. Patients also recorded disruption caused by their panic disorder using the Sheehan Disability Scale, SD total, (Sheehan 1986). This is a simple measure of social functioning which assesses disruption to daily lifestyle and comprises three 10 point subscales where patients self-rate disruption to work, social life, and family/home life. For the purposes of the current analysis a total score on the SD, representing the sum of the scores on the three scales was used.

7.3. Results

7.3.1. Statistical Analysis

Data were checked for abnormalities of distribution, presence of outliers, and multicollinearity.

Relationships between variables were also investigated by examining Pearson r correlations. Whilst there were intercorrelations amongst the data, no bivariate correlation exceeded 0.70, and thus no variables were excluded from the analysis on these grounds (Tabachnick & Fidell 1996). The distributions for the panic attack variables, Total Frequency, and Total Mean Duration were highly positively skewed (i.e. skew > 1.0, c.f. Ferguson & Cox 1993) and thus logarithmic transformations (Log 10 (variable + 1)), were performed on these variables, as described in Chapter 6. As goodness of fit tests which compare observed with expected

frequencies were to be used, adequacy of expected frequencies was checked and found to be within acceptable limits. No other operations on data were required.

The study design entails an investigation of the relationship between a dependant variable, dichotomised in terms of clinical significance of outcome, and a series of predictor variables measured at pre-treatment, in an attempt to identify predictors which discriminate between the clinically significant, and non-significant groups at post-treatment. Discriminant function analysis was deemed unsuitable for this purpose for a variety of reasons. Firstly, the predictor variables included a mix of continuous and categorical measures, and secondly, group sizes (clinically significant vs. non-significant), were, at times, very unequal. It was also expected that the distribution of the responses on the dependant variable would be non-linear with one or more of the predictor variables. That is to say, the probability of a patient being clinically significantly improved following treatment may be affected very differently by, for example, a 10 point change in rated anxiety over treatment depending on where across the range of potential anxiety scores this 10 point change occurred. A reduction of 10 points on an initial score of, for example, 15 points is highly likely to be a clinically significant change, whereas a 10 point reduction in an initial score of, say 30 points, is much less likely to represent a clinically significant improvement. In this example the relationship between group allocation and rated anxiety level would be described as non-linear. These factors violate the assumptions underlying discriminant function analysis and an alternative strategy of analysis is required. Logistic regression was therefor selected as the appropriate statistical technique (Tabachnick & Fidell 1996), as this technique is more flexible and does not require that the predictors be normally distributed, linearly related, or of equal variance within each group. Data were analysed employing logistic regression using the SPSS-X statistical package. Outcome was dichotomised as clinically significantly improved = 1, versus not clinically significantly improved = 0. The sample was dichotomised at treatment end-point (Day 84), on four separate criteria, namely, clinically significant improvement vs. non-improvement separately on each of the HAM-A, SRT, and FQ-AG, and also on a composite Day 84 responder criteria which required clinically significant improvement on all three outcome variables (HAM-A, SRT, FQ-AG) for a patient to be classified as a Day 84 responder. The sample was dichotomised again at 6 month follow-up, again on the same four criteria,

(clinically significant improvement on 6 month follow-up HAM-A, SRT, FQ-AG, and 6 month FU responder) with the added restriction in each case that the clinically significant improvement had occurred in the absence of intervening treatment during the follow-up phase. Separate logistic regression analyses were performed for each of these eight dependant variables.

Logistic regression permits several assessments of statistical significance. The significance of the contribution of individual predictors is assessed using the Wald Chi-Square test, which is noted as a particularly conservative criterion (Norusis 1990). Results for individual predictor variable are also reported as the log coefficients, Beta, and, standard error of Beta. A figure is also given for exponentiated Beta (Exp (B)). Sometimes known as the odds ratio, exponentiated Beta indicates the increase (or decrease) in odds of being in one outcome category when the value of the predictor variable is increased by one unit of measurement. As most of the predictor variables in the present study showed negative relationships with the outcome group clinically significantly improved, the values for exponentiated Beta are less than 1. Thus the smaller the value for Exp (B), for a particular predictor variable, the greater the influence of small changes in that variable on membership of the clinically significantly improved group. If a predictor variable has an Exp (B) value of, for example, 0.5, this means that an increase of one unit of measurement in this variable will reduce by half (0.5) the patients chances of being in the clinically significantly improved group. The adequacy of models constructed by logistic regression can be further tested in a variety of goodness of fit combinations, the most commonly used of these being firstly, a comparison of the devised model with a model containing the constant only (reported in SPSS as "model chi-square"). A finding of significant difference in this comparison indicates that the predictor variables in the model are contributing significantly to the prediction of outcome. A second combination involves a comparison of the devised model with the "perfect" or "hypothetical" model (reported in SPSS as " -2 log likelihood"). The perfect model is hypothesised to contain exactly the right set of predictors to duplicate the actual observed frequencies. A finding of non-significance of difference in this comparison represents a strong endorsement of the devised model as an equally adequate set of predictors as the hypothesised or perfect model. As a control for intercorrelation amongst variables, the predictor variables were entered into

the analysis sequentially, in the same order for each analysis. The first predictor variable entered was a control variable for treatment received. Treatment group was coded as a dichotomous variable as active (FL, FL+CBT, PL+CBT, CBT) versus inactive (PL), treatment. This variable reflected the findings of the main study (Sharp et al 1996, Chapter 4) where all active treatments showed a significant superiority over the placebo group (PL), and no statistically significant differences between the active treatment groups themselves on the main outcome variables (HAM-A, SRT, FQ-AG). Entering the treatment variable as the first predictor variable in the analysis permits the assessment of the predictive power of the other variables relative to the contribution of treatment to clinical outcome. This is an essential step in analysing data from a treatment outcome study. Other predictor variables were entered next, in the following order, first demographic predictors, age, sex, duration of current episode, and psychiatric history, then the panic attack variables, total frequency, total mean severity, and total mean duration, followed by the complaint-related variables, HAM-A, SRT, FQ-AG, and MADRS, and lastly the personality and social variables, ASI, SocMal, E, N, and SD total. Predictor variables were retained in the model if, at their stage of entry they showed a significant Wald test ($p < 0.05$) indicating the significance of that particular predictor variable, and also a significant difference ($p < 0.05$) for the model comparison with the constant only model indicating that the model including this variable had predictive advantages over a model containing the constant only. Any predictor variable that failed to achieve these criteria was discarded from the analysis. Results are reported for significant predictors only.

7.3.2. Treatment end-point (Day 84) results

Patient numbers for clinically significantly improved versus non-significantly improved for each outcome variable at Day 84 were, HAM-A, 119 vs. 30, SRT, 55 vs. 94, FQ-AG, 109 vs. 40, and Day 84 Responder, 53 vs. 96. Tables 7.1.1. to 7.1.4. show the significant predictor variables for each outcome variable. From these tables it can be seen that all four outcome variables showed high accuracy of prediction with between 71.9% and 84.5% of patients being correctly classified as achieving significant or non-significant improvement, with the highest predictive accuracy being found for membership of the significantly

improved groups. Also, for all four outcome variables the constructed model was significantly different from the constant only model, but not significantly different from the perfect model, indicating that the predictive models for the Day 84 end-point outcome were strongly predictive and approximated the best possible prediction of clinically significant outcome. Results for each outcome variable varied, with different predictors significant for each outcome variable.

For Day 84 HAM-A, (Table 7.1.1.) treatment group, SRT, and EPQ-E, were significant predictors indicating that lower levels of self-rated anxiety (SRT), and higher levels of extraversion (EPQ-E), along with receiving active treatment disposed towards clinically significant change in therapist rated anxiety at end-point.

Table 7.1.1. Prediction of treatment end-point (Day 84) clinically significant improvement on HAM-A.

HAM-A	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % correctly Classified
	Treatment Group	-1.277	0.277	21.23	0.0001	0.278	
	SRT	-0.043	0.015	7.77	0.005	.957	
	EPQ-E	0.131	0.052	6.29	0.01	1.137	**84.5%**

Perfect Model Chi-Square = 111.52, d.f. = 145, n.s.

Constant Model Chi-Square = 40.87, d.f. = 3, $p < 0.0001$

The values for Exp (B) indicate that treatment group (Exp (B) = 0.278) had the greatest influence on membership of the clinically significantly improved group, with an increase of one unit on this measure reducing a patient's odds of being in the clinically significantly improved by approximately 72%. With SRT and EPQ-E showing values closer to 1, larger changes on these measures would be predictive of change from the significant outcome group. This is only to be expected as treatment group represents a dichotomised variable (active vs. inactive treatment), thus a one unit change on this measure represents a complete change of treatment received, whereas both the SRT, and EPQ-E are continuous measuring scales with much larger potential ranges of scores. It is reasonable therefor, to expect changes in scoring larger than one unit to be required to influence outcome results.

For Day 84 SRT (Table 7.1.2.), treatment group, total panic frequency, and SRT, were significant predictors, indicating that a lower frequency of panic episodes (both panic attacks and limited symptom attacks), lower levels of self-rated anxiety (SRT), and receiving active treatment all disposed towards clinically significant improvement in patient self-rated anxiety. Total panic frequency had the greatest influence on membership of the clinically significantly improved group (Exp (B) = 0.237) with an increase in one unit on this measure reducing the odds of being in the clinically significantly improved group by approximately 76%. Treatment group showed a lesser effect on membership of the clinically significantly improved group (Exp (B) = 0.618). SRT showed the least influence on clinically significant improvement (Exp (B) = 0.96).

Table 7.1.2. Prediction of treatment end-point (Day 84) clinically significant improvement on SRT.

SRT	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	Treatment Group	-0.481	0.272	3.22	0.05	0.618	
	Total Panic Frequency	-1.437	0.599	5.75	0.01	0.237	
	SRT	-0.041	0.141	8.33	0.005	0.960	**76.0%**

Perfect Model Chi-Square = 163.65, d.f. =145, n.s.

Constant Model Chi-Square = 27.64, d.f. =3, $p < 0.0001$

For Day 84 FQ-AG (Table 7.1.3.), treatment group, and patient self-rated agoraphobic avoidance (FQ-AG) were significant predictors.

Table 7.1.3. Prediction of treatment end-point (Day 84) clinically significant improvement on FQ-AG.

FQ-AG	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	Treatment Group	-1.012	0.273	13.74	0.001	0.363	
	FQ-AG	-0.103	0.020	26.72	0.0001	0.901	**79.2%**

Perfect Model Chi-Square = 129.48, d.f. =146, n.s.

Constant Model Chi-Square = 43.86, d.f. = 2, $p < 0.0001$

Thus only receipt of active treatment, and lower initial levels of rated agoraphobic avoidance were related to clinically significant improvement in agoraphobic avoidance at treatment end-

point, with treatment group being by far the more influential of the two predictors. Receiving inactive treatment reduced a patients chances of being in the clinically significantly improved group by approximately 64%.

For the composite outcome variable Day 84 Responder (Table 7.1.4.), membership of the clinically significant outcome group was predicted by treatment group, total panic frequency, patient self-rated anxiety (SRT), and level of social maladjustment (SocMal). The direction of the relationship between outcome group and the treatment group, panic attack, and SRT predictors was identical to that found for the individual outcome variables (HAM-A, SRT, FQ-AG). The additional predictor variable, SocMal (Exp (B) = 0.715), indicated that increased levels of social maladjustment at treatment entry disposed against membership of the clinically significantly improved group. With an increase in one unit on the SocMal measure reducing a patient's chances of being in the clinically significantly improved group by approximately 30%. As for the SRT outcome variable, total panic frequency (Exp (B) = 0.298) was the most potent predictor, with treatment group and SocMal occupying an intermediate position with SRT (Exp (B) = 0.975), the weakest of the four predictor variables. Thus much larger increases in scores on SRT would be needed to reduce a patients chances of being in the clinically significantly improved group at treatment end-point.

Table 7.1.4. Prediction of treatment end-point (Day 84) clinically significant improvement on Day 84 Responder criterion.

Day 84 Responder	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	Treatment Group	-0.642	0.285	5.06	0.05	0.525	
	Total Panic Frequency	-1.209	0.599	4.07	0.05	0.298	
	SRT	-0.240	0.014	3.122	0.05	0.975	
	SocMal	-0.335	0.155	4.64	0.05	0.715	**71.9%**

Perfect Model Chi-Square = 160.76, d.f. = 141, n.s.

Constant Model Chi-Square = 29.38, d.f. = 4, $p < 0.0001$

The only predictor variable common to all four analyses was treatment group, the generally low values for Exp (B) for this predictor attesting to the obvious relationship between receiving active treatment and achieving clinically significant improvement. Indeed receiving inactive treatment reduced the odds of being in the clinically significantly improved group at Day 84 by between 38% and 71% depending on which outcome measure was used.

7.3.3. 6 month follow-up results

A total of n = 126 patients (out of a possible n = 149) attended for 6 month follow-up assessment. The numbers for clinically significantly improved without intervening treatment versus non-significantly improved for each outcome variable were, HAM-A 70 vs. 56, SRT 40 vs. 86, FQ-AG 65 vs. 61, and 6 Month follow-up responder 37 vs. 89. Tables 7.2.1. to 7.2.4. show the significant predictor variables for each outcome variable. From these tables it can be seen that the strength of prediction continued clinically significant improvement at 6 month follow-up was reduced compared to the Day 84 analyses. From 61.6% to 68.3% of patients were correctly classified as achieving clinically significant or non-significant improvement at 6 month follow-up, with the highest predictive accuracy being found for membership of the non-significantly improved groups. The reduced efficacy of the follow-up predictions was also suggested by the fact that, with the exception of the composite 6 Month FU Responder outcome variable, all analyses showed significant differences between the constructed models and both the constant only model and the perfect model. This indicates that whilst the constructed models were a significant improvement on the constant only model, they nonetheless did not represent the optimum prediction of outcome. There are therefor likely to be further influences on achievement of clinically significant improvement at follow-up which were not picked up by the predictor variables employed in this study.

Regarding models constructed here, for 6 Month HAM-A (Table 7.2.1.), membership of the significantly improved group was predicted by treatment group, and initial therapist rated depression level (MADRS). This suggests that patients with initially high levels of depression are less likely to achieve clinically significant improvement at follow-up, although with Exp (B) = 0.91, this is not a powerful relationship. Treatment group was also a stronger predictor

(Exp (B) = 0.652), with receipt of inactive treatment reducing the odds of being in the clinically significantly improved group by around 35%.

Table 7.2.1. Prediction of 6 month follow-up clinically significant improvement on HAM-A

HAM-A	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	Treatment Group	-0.426	0.218	3.82	0.05	0.652	
	MADRS	-0.093	0.044	4.53	0.05	0.910	**63.8%**

Perfect Model Chi-Square = 194.44, d.f. = 122, $p < 0.005$

Constant Model Chi-Square = 9.14, d.f. = 2, $p < 0.01$

For 6 Month SRT (Table 7.2.2.), only one predictor variable, total panic frequency, was significant indicating that a high frequency of panic and limited symptom attacks at the outset of treatment disposed to membership of the non-significantly improved group. The Exp (B) value of 0.398 indicating that an increase in one unit on this predictor variable would reduce the odds of being in the clinically significantly improved group at 6 month follow-up by around 60%.

Table 7.2.2. Prediction of 6 month follow-up clinically significant improvement on SRT.

SRT	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	Total Panic Frequency	-0.921	0.494	3.46	0.05	0.398	**61.6%**

Perfect Model Chi-Square = 187.75, d.f. = 124, $p < 0.01$

Constant Model Chi-Square = 3.54, d.f. = 1, $p < 0.05$

For 6 Month FQ-AG (Table 7.2.3.), treatment group and patient self-rated agoraphobic avoidance (FQ-AG) were significant predictors. Thus clinically significant improvement at follow-up on FQ-AG was predicted by the same predictor variables at treatment end-point (Day 84), and 6 month follow-up. The similar Exp (B) values suggest that FQ-AG has much the same influence on group membership at Day 84 and 6 month follow-up, whereas the influence of treatment group was reduced at follow-up as indicated by the increased Exp (B) value.

Table 7.2.3. Prediction of 6 month follow-up clinically significant improvement on FQ-AG.

FQ-AG	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	Treatment Group	-0.507	0.223	5.18	0.05	0.601	
	FQ-AG	-0.033	0.14	5.62	0.01	0.966	**63.8%**

Perfect Model Chi-Square = 195.39, d.f. = 122, $p < 0.01$

Constant Model Chi-Square = 10.35, d.f. = 2, $p < 0.005$

For the composite follow-up outcome variable, 6 Month FU Responder (Table 7.2.4.), only social maladjustment (SocMal) was a significant predictor, and showed a moderate influence on group membership (Exp (B) = 0.671), with an increase in one unit on this measure reducing the odds of clinically significant improvement by 33%.

Table 7.2.4. Prediction of 6 month follow-up clinically significant improvement on 6 month FU responder criterion.

6 Month FU Responder	Variable	B	S.E.	Wald	Sig	Exp (B)	Overall % Correctly Classified
	SocMal	-0.397	0.187	4.52	0.05	0.671	**68.3%**

Perfect Model Chi-Square = 136.63, d.f. = 124, n.s.

Constant Model Chi-Square = 5.19, d.f. = 1, $p < 0.05$

Importantly however, 6 Month Follow-up Responder was the only follow-up outcome model which yielded a non-significant result in the comparison with the perfect model. The 6 Month FU Responder model also showed the highest percentage of patients correctly classified (68.3%) of all the follow-up models. Thus prediction of which patients will achieve clinically significant improvement on all three outcome measures (HAM-A, SRT, FQ-AG), without receiving any intervening treatment during the follow-up period is adequately predicted by level of social maladjustment at treatment entry, with high levels of social maladjustment disposing against clinically significant improvement.

7.4. Discussion

It is worth recognising at the outset that regression analyses of the sort presented here are highly sensitive to variations in sample size and configuration, the nature and type of measure used, and intercorrelation between variables and consequent order of entry effects. The fact that the logistic regression employed here is more robust than other forms of regression analysis notwithstanding, the above, and other restrictions, mean that the findings of the present study should be regarded as, at best, provisional, and certainly requiring replication. The more so because the current study is the first to employ a logistic regression with treatment outcome data from patients with panic disorder and agoraphobia and results are therefor best seen as preliminary. Furthermore, regression analyses on treatment outcome results are not only vulnerable to the structure of the analysis itself, but also to the effects of the treatments investigated. As already argued, treatment received should be coded as a predictor variable and preferably entered first into the analysis. If this is not done the influence of treatment on outcome cannot be accounted for. This influence will also vary depending on the efficacy or potency of any given treatment. A powerfully effective treatment which brings about clinically significant changes in patients regardless of initial severity of problem, or other social or personal factors is likely to leave little variance in outcome to be explained by other non-treatment related factors. On the other hand, outcome following a weak or partially effective treatment may be strongly influenced by non-treatment factors such as personality or other social or demographic variables. Thus any regression analysis on treatment outcome results cannot easily be divorced from the treatments that produced those outcomes, and such treatments should be borne in mind when interpreting the results from these regression analyses.

Moving on to consider the results of the present study, the first finding of note, concurrent with previous studies (Jansson et al 1987, Keijsers et al 1994), is that few of the predictor variables entered into the analysis yielded significant results. Demographic variables were found to have no predictive utility. This is again in keeping with previous studies (Jansson et al 1987, Chambless & Gracely 1988) which found no relationship between patient demographics and treatment outcome. Such findings attest to the wide clinical utility of treatments for panic disorder and agoraphobia in that they are not apparently restricted by

considerations of age, gender, and so forth. Panic attack variables were significant predictors in only three of the eight regression analyses (Day 84 SRT, Day 84 Responder, 6 Month FU SRT). For these three outcome variables they were however highly influential predictors, showing smaller values of Exp (B) than any other predictor variables. This was for total panic frequency only, neither the severity or duration measures were retained in any of the analyses. Nonetheless, the frequency of panic and limited symptom attacks pre-treatment appears to be a powerful predictor of subsequent treatment outcome.

Personality variables showed little predictive utility. Previous studies that had investigated personality had concentrated on personality psychopathology. In the current study the explicit aim was to investigate more broadly based personality dimensions. No significant findings were found for the Neuroticism scale of the EPQ, nor were there any significant findings for the ASI which is argued to be a specific and sensitive predictor of panic sensitive personality (McNally 1994). This latter result is contrary to expectation and requires some explanation. Previous predictive studies (Chambless & Gracely 1988, Keijsers et al 1994) have found measures tapping agoraphobic catastrophic cognitions, or other fear of fear variables, to have predictive utility, and have suggested that these findings are in keeping with cognitive explanations of panic disorder (e.g. Clark 1986). Such a relationship between fear of fear, as measured by the ASI, and treatment outcome was absent in the present study. There are two potential explanations for this both of which may have operated with the current data set. Firstly the effect of the ASI in the analysis may have been reduced due to intercorrelation with other variables and it's late entry into the analysis. Indeed ASI did show moderate correlations with HAM-A, SRT, and FQ-AG, all of which were entered into the analysis before the ASI. A second explanation refers to actual treatments used in the study. The studies which found significant effects with fear of fear type variables (Chambless & Gracely 1988, Keijsers et al 1994) both employed behavioural exposure based treatments. These treatments would not therefor have focused directly on cognitions and cognitive change. Thus variance existing between the dispositional variables and treatment outcome may only have been minimally effected by such treatment interventions thus a predictive relationship was found. The present study employed a cognitive behavioural treatment (CBT) which was much more directly targeted at cognitive change, and also a medication treatment,

the SSRI fluvoxamine, which has also been shown to bring about cognitive change (Weinstein & Nutt 1995). Thus all of the active treatments in the present study will have exerted a significant effect on treatment outcome in terms of cognitive change and as such are likely to have obscured any relationship between the ASI and treatment outcome. This suggested effect of treatment would have been all the more powerful if large quantities of the predictive variance of the ASI had been further taken up by other variables entered earlier in the analysis such as the HAM-A, SRT, or FQ-AG. In this analysis the ASI added no predictive utility over that supplied by the more commonplace clinical measures of general anxiety and agoraphobic avoidance.

Regarding the findings of significant relationships between predictor variables and clinical significance of outcome, firstly prediction of outcome was not achieved by a single consistent predictor variable or even a small number of predictor variables. This is not surprising really as, to echo Keijsers et al (1994), if one, or even two or three, such consistent predictors existed it is unlikely that 15 years of research could have been conducted without their being identified. It is clinically more credible that a range of predictor variables exist with a range of relationships to differing outcome variables. An individual patient's chances of being a treatment success or failure will be related to the number and pattern of these predictors operating in their case. The pattern of results in the present study is one of variety of predictors across outcome variables and across occasions of measurement, and as such is in keeping with previous research. The tests of adequacy of the obtained models which is possible within logistic regression yielded informative results with all of the models derived from the Day 84 analyses being an adequate representation of the actual observed frequencies for outcome group membership (clinically significantly improved vs. non-improved) and large proportion of patients were correctly classified in each analysis. At treatment end-point (Day 84) one predictor was consistently related to all four outcome variables, namely treatment group (active vs. inactive). That is to say, the most consistent determinant of whether the patients in this study achieved clinically significant improvement immediately following treatment was whether they received active or inactive treatment. This finding makes clinical sense and is in keeping with the considerable evidence presented thus far (Sharp et al 1996, Chapter 4, Sharp et al 1997b, Chapter 5) indicating the significant

advantage of the active over the inactive treatments employed in this study. The finding of significance for treatment group is also relevant to the forgoing discussion of the importance of considering the relative power or efficacy of the treatments used when interpreting the results of regression analyses on treatment outcome data. To avoid the problem of over prediction as a result of small sample sizes, the treatment groups were subdivided only as active versus inactive treatment in the current analysis. The estimation of the predictive value of each treatment individually was not therefor possible. The investigation of this interesting area will require further research employing much larger sample sizes.

Some of the initial complaint-related variables employed in this study showed some promise as predictors of clinically significant improvement. This again is reassuring to the research clinician, suggesting that the measures of general anxiety and agoraphobic avoidance employed as treatment outcome measures actually show a relationship to outcome when used as predictor variables in regression analyses. Patient rated measures of general anxiety, SRT, and agoraphobic avoidance, FQ-AG, were significant predictors although it is clear from the odds ratios (Exp (B)) for these variables that fairly large changes on these measures would be required to influence group membership. Interestingly, these variables showed significant results for their related outcome measures only. That is, the anxiety based outcome variables of clinically significant improvement on the HAM-A, and SRT, were both predicted by initial level of patient self-rated anxiety on the SRT, whereas clinically significant improvement in agoraphobic avoidance on the FQ-AG, was predicted by initial scores on the FQ-AG. The predictive value of self-rated anxiety has been noted in previous studies (Jansson et al 1987) as has the relationship between good treatment outcome in terms of agoraphobic avoidance and low initial scores on measures of agoraphobia (Chambless & Gracely 1988, Fischer et al 1988, Keijsers et al 1994). Neither of the therapist-rated variables, the HAM-A for anxiety or the MADRS for depression showed any significant relationship with outcome at treatment end-point (Day 84). Variables related to panic attacks did show significance as predictors for the SRT and Day 84 Responder composite outcome measures, with higher pre-treatment frequencies of panic attacks plus limited symptom attacks disposing towards non-significant change at treatment end point. This finding does lend some support to the view that frequency of panic attacks is an important defining feature

of panic disorder. Panic attack variables have been shown to be significant predictor variables in other studies (Jansson et al 1987), this is however the first time that panic attack variables recorded using a prospective event recording method, and thus less effected by retrospective bias, have been used as predictors in a regression analysis. The expected reduction in reported frequency of panic attacks due to the prospective recording does not seem to have removed the significance of panic frequency as a potentially useful predictor. The significant finding for total panic frequency is also in accord with the observed trend amongst predictor variables relating to initial severity of complaint, that the more severe the initial complaint the less the likelihood of achieving clinically significant improvement. Treatment outcome at Day 84 was also predicted by two other variables. For the HAM-A outcome variable the extroversion score, E, from the EPQ, showed a significant value suggesting that more extrovert patients were more likely to achieve clinically significant improvement on the HAM-A. The converse of this being of course, that more introverted individuals will fair less well. This finding is noteworthy, as it is an indication that personality assessed as a general disposition may have some bearing on treatment outcome. It may be the case however that, given that there was a single therapist, this finding may reflect a therapeutic relationship factor, that is, the therapist worked better with extroverts. Consideration should be given in future to including measures of "normal" personality variables in treatment outcome studies rather than including only assessments of personality disorders as has been the case until now. For the Day 84 Responder outcome variable group membership was also predicted by the measure of social maladjustment (SocMal). This indicates that membership of the strictly defined group who achieve clinically significant improvement on all three outcome measures (HAM-A, SRT, FQ-AG) is partly defined by the level of social disruption in patients lives at the start of treatment. This reinforces the commonly held clinical wisdom that those patients with more ongoing life events or hassles fair less well in treatment. Overall for Day 84 treatment end-point assessment, results of this study suggest that higher patient self-ratings of pre-treatment severity, lower levels of extroversion, and the presence of multiple social problems all militate against a positive treatment outcome. Armed with such information the clinician may be more able to appropriately monitor the progress of "at risk" patients and provide remedial intervention if required. Further study will be required to ascertain whether the provision of such remedial intervention will actually result in further clinical improvement. Unrestrained optimism is perhaps inappropriate, given that some investigations with panic

disorder patients (Brown & Barlow 1995) have suggested that the provision of extra treatment to treatment non-responders does not consistently result in further improvement.

An inspection of the pattern of findings for the prediction of clinically significant improvement at 6 month follow-up reveals a reduced number of significant predictor variables, lower proportions of patients correctly classified, and only one of the four prediction models (6 Month FU Responder) showing a non-significant comparison with the perfect model. Thus prediction of clinically significant improvement at 6 month follow-up was not achieved with the same degree of success as prediction of outcome at treatment end-point. The significant differences found between the models derived from this analysis and the so-called perfect models suggest that a proportion of the variance in outcome at 6 month follow-up is not predicted by the full set of predictor variables entered into the analyses used here, and that other factors unmeasured in this study, influence outcome at follow-up. Further research is obviously required to discover the nature of other possible predictors and to assess their influence on outcome at follow-up. As an example of such other possible predictors, in the present study social maladjustment was formally assessed at treatment entry only, thus no record was available of any major life events or social disruption occurring during the follow-up period. This is a potentially important variable which should certainly be investigated in further. Treatment group remained a significant predictor at follow-up for HAM-A and FQ-AG only. Thus the importance of which treatment (active vs. inactive), was no longer a significant influence on follow-up outcome as indexed by patient rated anxiety, SRT, and 6 Month FU Responder variables. Clinically significant improvement at follow-up on the SRT outcome variable was predicted by total panic frequency only, this being a continuation of the significance shown at Day 84 for this predictor. The FQ-AG outcome variable showed the same predictors at follow-up as at Day 84, namely treatment group and initial FQ-AG. For the composite outcome measure 6 Month FU Responder only social maladjustment (SocMal), was retained as a significant predictor. This was the only follow-up outcome variable to show an insignificant Chi-Square in the perfect model comparison suggesting that SocMal represents an adequate predictor of the observed frequencies of outcome group membership for this variable. Thus number of social problems at treatment entry has a significant bearing on whether patients achieve clinically significant improvement

on a strict index which requires clinically significant change on all three target measures (HAM-A, SRT, FQ-AG) and no intervening treatment during the follow-up phase. This finding taken together with the significant finding for SocMal for Day 84 Responder outcome, suggests that level of social disruption is an important predictor. The only significant predictor variable at follow-up that had not shown significance at Day 84 was initial depression score on the MADRS which was a significant predictor for clinically significant improvement on the HAM-A. Several previous studies have found no relationship between outcome at treatment end-point and initial depression level (Chambless & Gracely 1988, Fischer et al 1988, Keijsers et al 1994), as did the present study. It appears however that initial depression level may have some bearing on follow-up results with patients with higher initial levels of depression being less likely to achieve clinically significant improvement on the HAM-A at 6 month follow-up.

The current study represents an initial investigation of the value of possible prognostic indicators of treatment outcome. In an attempt to increase the clinical relevance of results, outcome was defined in dichotomised groups using theoretically grounded measures of clinically significant improvement. The use of the Jacobson procedures in this study did result in particularly stringent criteria of clinically significant improvement for the SRT, and consequently for the Day 84 Responder criteria which required clinically significant improvement on all three outcome measures. The follow-up outcome measures were further restricted by the requirement that no intervening treatment should occur during the follow-up period. These requirements may have led to rather restricted groups in some cases and thus the generalisability of the findings may be compromised to some extent. The use of the Jacobson procedures was, however, deemed to be of more relevance to wider clinical practice than an investigation focused solely on variance accounted for in outcome scores, or the dichotomisation of outcome groups according to non-standardised or idiosyncratic procedures. Logistic regression was employed to identify predictor variables that influenced membership of outcome groups. Significant results were obtained with the most influential predictor variables (smallest values for Exp (B)), being treatment group, and total panic frequency. It is worth noting that, of the significant predictor variables, treatment group and total panic frequency were entered first and second in the analyses, and some of their power

as predictor variables may be attributable to this early entry to the analysis. In general the findings from the present study provide some reassurance for clinicians to the extent that predictive validity was shown for measures taken as standard in clinical practice. Thus frequency of panic attacks, general anxiety, agoraphobic avoidance, and level of depression all showed some influence on outcome. The significance of other predictors such as social maladjustment, and extroversion show however that other influences on treatment outcome should be considered. Of course, indications of significance in regression analyses such as this do not denote direct causal relationships. More controlled experimental study will be required to investigate and define the nature of the relationships between treatment outcome and the potential predictors found in this study. The present study has been reported elsewhere as Sharp et al (Submitted).

CHAPTER 8 DISCUSSION

8.1. Discussion

Chapter 1 of this thesis discussed the development of the clinical concept of panic disorder and agoraphobia, it's classification, and suggested antecedents and consequences. Chapter 1 also discussed the development of pharmacological and psychological treatments for panic disorder and agoraphobia and the investigation of their comparative efficacy using techniques such as meta-analysis. Following this discussion, it was argued that greater scientific control was required in studies comparing pharmacological and psychological treatments for panic disorder, and that further comparative studies were required. It was suggested that a current and informative study would be one investigating the relative and combined efficacies of the most recently developed and most promising pharmacological and psychological treatments. A study investigating the treatment efficacy of the SSRI fluvoxamine, and the psychological treatment, cognitive behaviour therapy was therefor conducted. This study was designed following a thorough review of previous treatment outcome study methodology, reported in Chapter 2. This critical review assessed the adequacy of treatment outcome study design, in terms of both necessary scientific controls and the need for studies to produce relevant and clinically meaningful results. Balancing the, at times conflicting, demands of research and clinical practice inevitably means that compromises are made in study design. These compromises, discussed in detail in Chapter 2, relate not only to the actual conduct of treatment outcome studies but also, as a first step, to the recruitment and construction of the experimental sample of patients who will receive the treatments. If results from a well designed study are to be applicable to wider clinical practice they must arise from a sample which is as representative as possible of the patients seen in wider clinical practice. Factors affecting the representativeness of the sample employed in the present studies will be discussed next with particular emphasis on inclusion/exclusion criteria, classificatory systems, referral source, and study setting.

The requirement that patients fulfil stipulated inclusion/exclusion criteria prior to entry to treatment is a potentially confounding factor. If large numbers of patients were referred for the present studies but were not permitted entry on these criteria, the overall

clinical representativeness of the results would have to be questioned. Some previous studies have employed inclusion/exclusion criteria which led to up to 70% (Clark et al 1994), of the patients referred for study treatment being rejected. Fortunately, of the n = 238 patients referred for inclusion in the studies reported here, only n = 45 (18.9%) were excluded as unsuitable, and the sample was not therefor heavily skewed by restrictive inclusion/exclusion criteria. It should be noted however that the figures above give no indication of the number of patients whom general practitioners might have considered suitable for referral for either pharmacological or psychological treatment but nonetheless did not refer for entry assessment. As GPs were not requested to keep a record of patients considered potentially suitable but not referred, no conclusions can be reached on this subject. Such a record could be kept in future studies as part of the process of establishing the representativeness of research populations. One inclusion/exclusion criterion that may have caused problems was the requirement that patients should be free from concurrent psychotropic medication for 28 days prior to study entry. It is not known how many patients were offered study referral by their GP but declined on the grounds that they did not wish to discontinue medication or because they actively preferred pharmacological treatment provided by their GP as an alternative to study referral. Patients may also not have been offered referral if their GP considered them unlikely to be able to discontinue concurrent psychotropic medication. Of the patients actually referred for study entry, n = 5 patients were referred whilst taking psychotropic medication which they declined to discontinue for the required 28 day wash-out period. Further research is again required to investigate possible differences between patients taking concurrent psychotropic medication and those who are not, and to investigate the ramifications of any differences for treatment responsiveness and thus influence on study results. Data collected by the current author subsequent to the present studies may provide the opportunity to investigate this. A series of patients with DSM III-R panic disorder and agoraphobia were treated with CBT to the same protocol as that used in the present studies. A proportion of these latter patients continued taking concurrent psychotropic medication whilst receiving the CBT. Thus the potential influence of concurrent psychotropic medication on CBT might be assessed. Further

data will be required if the effects of concurrent psychotropic medication on pharmacological treatments are to be investigated.

The present research was conducted using the DSM III-R classificatory system, as DSM IV was not yet published when the present treatment study began recruiting. There are differences between DSM III-R and DSM IV that need to be considered. The major difference between the two classificatory systems is that DSM IV requires a frequency criterion (recurrent panic attacks) and, a fear of recurrence criterion (persistent fear of recurrence of panic attacks or avoidance or other alteration of behaviour as a result of panic attacks), before a classification of panic disorder is permitted. In DSM III-R, on the other hand, either the frequency, or the fear of recurrence criteria alone would permit a classification of panic disorder. Patients could therefor be classified as suffering from panic disorder if they had only one panic attack followed by at least one month of persistent fear of recurrence. Thus it is possible that under DSM III-R many patients could be classified as panic disorder although they suffered panic attacks only very infrequently, and as such may not be representative of the wider population of panic disorder patients. It is also possible that these patients present a less severe form of the disorder, indeed severity of panic disorder is assessed in DSM III-R in terms of frequency of panic attacks. A large proportion of infrequent panickers in a study may therefor make the sample less representative of the wider clinical population. It is important to know how many of the patients in the present studies suffered from infrequent panic attacks, and thus achieved only one of the two classificatory criteria now required by DSM IV. These patients can be easily identified from their DSM III-R classificatory profiles and comprised n = 36 (18.6%) of the sample of n = 193 patients who entered treatment in the present studies. This proportion of the total number of patients entering treatment is unlikely to have had an undue influence on treatment outcome findings, or reduced the representativeness of the sample, given that by far the largest proportion of patients had more frequent panic attacks.

The patients treated in the present studies were all referred for treatment by their GP and received treatment in the primary care setting. These are both notable departures from previous study methodology where patients were often self-referred, or recruited

via advertisement, and received treatment in specialist hospital or university clinics. The first point has a bearing on the treatment responsiveness of the sample. As previously discussed in Chapter 2, Aronson (1987b) found self-referred patients to present with more chronic disorders and to be less treatment responsive than physician referred patients. The present sample may conversely, therefor, have been more treatment responsive than those of previous research. The present studies were conducted within the National Health Service where in wider clinical practice patients gain access to treatment only through referral by other agencies, most commonly GPs. It was a conscious decision in the present research to mirror standard Health Service practice regarding referrals rather than to emulate previous research practice. In this way findings from the present studies have more relevance to wider clinical practice which was deemed to be the more important focus. Regarding treatment setting, this was the first pharmacological vs. psychological treatment study on panic disorder and agoraphobia to be conducted in the primary care setting. It cannot be clear therefor whether the patients treated in the present study differed in any substantive way from those treated in previous studies conducted in larger institutions as no specific comparison of the two groups has ever been made. An interesting area where treatment setting may have influenced study results, however, relates to treatment drop-outs. In a review of drop-out rates from psychotherapy delivered in a variety of settings Hunt & Andrews (1992) reported that drop-out rates were around 8% in controlled explanatory studies delivered to restricted populations in research centres, and rose to circa 17-20% for treatments delivered in specialist centres. They noted however that drop-out rates rose to between 30-60% for psychotherapies delivered in community facilities. Thus, accepting firstly the large assumption that treatments were of equivalent quality in each facility, the setting in which a treatment is delivered may have a considerable influence on drop-out rate. As noted in Chapter 4, the CBT group in the main treatment study showed a high drop-out rate (32.2%, n = 13). This was suggested to be similar to the drop-out rates found for psychological treatments given in the absence of concurrent psychotropic medication in previous studies (Michelson et al 1985, 1990, Black et al 1993a), but higher than those reported in other studies of psychological treatments (Barlow et al 1989, Clark et al 1994).

The forgoing argument suggests that the conduct of the study in the primary care setting may also have operated to inflate the drop-out rate from CBT in the present study. The choice to conduct the studies in the primary care setting was again a conscious one and was taken once more to ensure the greatest overlap between study method and wider clinical practice, including factors such as treatment drop-out. The forgoing discussion indicates that whilst there may inevitably be differences between the experimental sample employed in the present studies, and the range of patients seen in wider clinical practice with panic disorder and agoraphobia, these have been minimised as much as possible, and the findings of the studies presented here can be related to wider clinical practice with some confidence.

The wider clinical implications of the findings of the studies conducted here will now be considered. Findings from the main treatment study (Chapter 4) indicated that all of the treatments studied showed statistically significant effects to some extent. This included the placebo group who received placebo medication plus balanced therapist contact but no active treatment advice or instruction. The results from this group (PL) constituted a strong placebo effect against which the active treatments were compared. Strong placebo responses have been reported fairly consistently with panic disorder patients (Mavissakalian 1988, Fossey & Lydiard 1990, Mellergard & Rosenberg 1990). Despite this evidence of efficacy, the placebo group showed the lowest levels of clinically significant improvement at treatment end-point, and the greatest requirement for additional treatment during the follow-up phase. What this means in clinical practice is that panic disorder and agoraphobia patients appear to be responsive to intervention and show some gains even with supposedly inert treatments such as placebo medication and simple therapist contact which provided the opportunity to describe current state and symptoms. It is possible therefor, that many interventions of differing focus, and indeed quality, may on initial inspection appear to be effective in panic disorder. To truly and accurately distinguish effective treatments for panic disorder and agoraphobia, however, careful measurement of the full range of the disorder, investigation of the clinical significance of results, and assessment of post treatment status at follow-up are all required. Using this approach the main treatment outcome study indicated that of the

active treatments, FL + CBT and CBT alone were the most consistently effective, with patients receiving FL+CBT showing a significant advantage over placebo earlier in treatment than the CBT alone group. The drop-out rate for patients receiving CBT alone was, however, higher than that for placebo + CBT. This finding affords the clinician the possibility of offering patients either a combined pharmacological and psychological treatment, with the possibility of an earlier treatment response, or, for those patients who express a preference not to take medication, the psychological treatment can be used alone with negligible loss of efficacy. The clinical usefulness of cognitive behaviour therapy is however limited by its availability (Lader 1994). The relative lack of trained clinicians available to offer CBT is a practical limitation to the usefulness of this treatment. In this context the finding of relative efficacy for the group receiving fluvoxamine alone suggests that this SSRI medication may represent a useful treatment in circumstances where treatments such as CBT are not available. It is true that the patients receiving fluvoxamine alone did show a weaker response on some measures (e.g. SRT), and there was some fall off in efficacy over the 6 month follow-up period. The substantial relapse and rebound rates found for other medications such as the benzodiazepine alprazolam (Pecknold et al 1988), were not found for fluvoxamine in the present study, or in other studies investigating withdrawal effects for fluvoxamine (Black et al 1993b). Also of considerable interest is the fact that the outcome results for fluvoxamine in the present study were obtained after a short 12 week trial of the medication followed by abrupt discontinuation. It is commonly suggested (Johnson et al 1995), that antidepressant medications used to treat panic disorder should be continued for 6-8 months before being gradually tapered. The current finding of efficacy for fluvoxamine in short-term use whilst interesting, should be treated with some caution. Patients receiving fluvoxamine alone in the current study also received balanced therapist contact and thus had treatment appointments substantially longer than the norm for a patient receiving a medication treatment in general practice. The true efficacy of fluvoxamine for panic disorder as it would be used in the primary care setting could only be assessed if a further group of patients were to be run to an identical treatment protocol to the current study with the exception of treatment appointments of a duration and frequency more typical of normal primary care practice. Ideally this group of patients would be run with

a double-blind placebo for medication. This secondary study would be an important addition to the findings reported thus far. The finding here of some short-term efficacy for fluvoxamine particularly when supported with therapist contact, nonetheless suggests a possible development in treatment service delivery. Patients receiving SSRI medications where full CBT treatments are not available could be provided with some form of psychosocial support if this were shown to have enhanced efficacy over the use of medication alone. This clinical approach of supported medication use may be achievable using personnel other than scarce clinical psychologists. A full investigation of such possible treatment approaches will, of course require a properly designed controlled study methodology.

The outcomes described above were all indicated across a wide range of assessments of patient and therapist report measures of anxiety, depression, and agoraphobic avoidance. The assessment strategy adopted in this study, of increasing the breadth of assessments employed, permitted a more detailed description of treatment outcome. This held true for most of the measures employed with the notable exception of the panic attack measures. It is clear from Chapter 6 that panic attack variables are not useful outcome variables proving to be responsive to all the interventions used and failing to discriminate between them. This finding would suggest that panic attack variables do not provide the best indication of treatment response and should certainly not be employed as the sole indication of outcome following treatment for panic disorder and agoraphobia, but should be used in combination with the other measures of anxiety, depression and agoraphobic avoidance which proved to discriminate better between treatments. This is a potentially important finding given the number of previous treatment outcome studies which have discussed findings in terms of changes in panic attack frequency, or more often proportion of patients panic attack free at treatment end-point. This note of caution to researchers holds equally well for clinicians. Improvements in panic attack patients should not be judged simply in terms of changes in panic attack frequency if an accurate picture of clinical response to treatment is to be gained. Chapter 4 also described outcome in terms of assessments of clinical significance. The trend towards the further description of treatment outcome results in

terms of their clinical significance is one which is now widely recommended (Shear & Maser 1994). The methods developed by Jacobson and colleagues (Jacobson & Truax 1991), used in Chapter 4, are derived from a statistical argument and thus have a more rational basis than other previous attempts to define clinical significance in terms of individual and different definitions of "high end-state functioning" (Barlow et al 1989, Michelson et al 1990, Clark et al 1994). Using the Jacobson methods of defining clinical significance of improvement in the main study led to a greater clarification of results and a clearer differentiation between treatment groups. This alone makes the inclusion of assessments of clinical significance an essential ingredient in any future treatment outcome study, and a potentially valuable addition to assessment in wider clinical practice. These assessments of clinical significance do have some problems however. The statistical strength of the Jacobson methods is also paradoxically their weakness. These methods of defining clinical significance of outcome whilst based on sound statistical reasoning requiring a shift away from the distribution of a clinical population, towards a non-clinical distribution, are nonetheless statistical rather than clinical criteria. Further work is required to compare the statistical measures of clinically significant improvement with more directly clinically relevant indices such as surgery attendance, medication use, referral to secondary care, and so forth. These latter indications of service usage were all shown to be inflated in panic disorder patients as compared with age sex matched controls (Simpson et al 1994). If a treatment is to be regarded as having a truly clinically significant impact one would expect a reduction in these service usage variables post treatment. Earlier, alternative, methods of assessing the clinical significance of treatment outcomes relied on the use of global measures of outcome completed by patients and relevant clinical personnel (Kazdin 1977, Strupp & Hadley 1977). These therapist and patient ratings of change following treatment have also been suggested to be more likely to relate criteria of clinically significant change to the social validity or personal relevance of that change (Baer 1988). Just such global measures were employed in Chapter 5, along with ratings of general psychiatric wellbeing, and social disruption also relevant to the assessment of the clinical significance of outcome. The study reported in Chapter 5 was designed to assess the viability of treatment

outcome measures designed to be more informative and more suitable for use in wider clinical practice, particularly in the primary care setting. The appropriate measurement of treatment outcome in everyday clinical practice has been the subject of some comment particularly as it applies to the primary care setting (King 1997). The study reported in Chapter 5 showed that patient and therapist report ratings of global outcome expressed as current distress and improvement since commencing treatment were valuable brief outcome indicators. The findings have additional intuitive appeal in that the individual undergoing the treatment, and the individual delivering it, agree with the more traditional outcome measures and with each other, on the progress being made in treatment. This agreement was also found for the ratings of general wellbeing and social disruption. It is clear therefor that these brief measures do function as acceptable indicants of treatment outcome and can therefor be recommended for use in wider clinical practice. It was also clear from Chapter 5 that further training of general practitioners may be required if they are to be included in the assessment process. The wider use in clinical practice of treatment outcome measurement, of any form, is likely to increase knowledge and understanding and would therefor be of considerable advantage.

The treatment outcome findings produced by the studies presented here can be considered with some confidence given the extent of the scientific controls adopted in the study designs. Results may also be generalised to wider clinical practice with a similar degree of confidence. It is fairly clear therefor that the psychological treatment, cognitive behaviour therapy, used here is a viable and generally effective treatment for the prevalent and disruptive condition that is panic disorder and agoraphobia. The recent interest in the SSRI antidepressants as potential pharmacological treatments for panic disorder has also been supported, although further work is needed to investigate the extent to which the efficacy shown here depended on the concurrent therapist contact given with the fluvoxamine and placebo medications in this study. The final investigation (Chapter 7) of this thesis attempted to take the discussion beyond straightforward treatment outcome by attempting an investigation of potential predictors of treatment response. In keeping with the overall aim of this thesis, to ensure relevance to clinical

practice, the study attempted the prediction of clinically significant treatment outcome rather than simple treatment response. Whilst essentially an exploratory study and as such requiring replication and expansion, some findings of relevance to wider clinical practice did emerge. Although panic attack variables were found in Chapter 6 to be indiscriminate treatment outcome variables, the pre-treatment frequency of panic attack plus limited symptom attacks was found to be a powerful predictor of treatment response. This finding was in keeping with the general trend in the analysis in Chapter 7 for poorer outcome to be predicted by higher pre-treatment scores on patient rated measures of anxiety and agoraphobic avoidance. Also of relevance clinically, were the significance of personality and social disruption measures in the prediction of treatment outcome. These latter findings reinforce the clinical wisdom that it is not only the disorder itself which is relevant to outcome, but also the person who is suffering from it, and the social circumstances in which they find themselves. The predictions for immediate treatment outcome were all strong and reasonably statistically sound. Further work is of course required to replicate these results and to further investigate the value of these variables as clinically useful outcome predictors. This might be achieved by including the significant predictor variables in a prospective study of their ability to identify treatment response. In contrast to the treatment end-point results, the predictions for outcome at follow-up were less sound, and it is clear that more work will be required to increase our understanding of the factors and processes which contribute to continued wellbeing after treatment is complete. Follow-up is indeed the area where more information on the present cohort of patients is definitely required. The 6 month follow-up period employed in the studies reported here is relatively short and further information on the continued status of the patients treated here would be of considerable interest. The present research findings would therefor be strengthened by a long term follow-up study. Such a study should pay close attention not only to patients' status at follow-up assessment but should also make an assessment of any post study treatment received. This could be best achieved by a methodology entailing a review of patients' GP case records. Such a method was employed in the study comparing panic disorder patients' service usage with that of age, sex matched controls (Simpson et al 1994) and

provides a record of patients' post treatment health service usage, thus permitting a truly clinically relevant assessment of post-treatment improvement. These longer term findings are necessary to fully assess the efficacy of the treatments studied here. In the short term however, it is hoped that the studies presented here have gone some way to providing further scientifically accurate and clinically relevant information on the treatment of panic disorder and agoraphobia. It is further hoped that the demonstration of treatment efficacy for panic disorder and agoraphobia in the primary care setting provided here will stimulate interest in the wider and more local provision of treatments for this prevalent and disruptive condition.

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APPENDIX I TREATMENT MANUAL

AGORAPHOBIA - PATIENT MANUAL

You have been told that you are suffering from agoraphobia and that what causes this problem is anxiety.

People who are suffering from agoraphobia feel frightened or panicky when they go far from home, or into crowded places, or on buses or trains. They often feel anxious and frightened if left on their own or if they feel they are far from help. When they feel frightened they may experience very strong and unpleasant physical feelings. These are feelings of fear, anxiety and panic.

The short description above probably doesn't tell you anything you don't already know very well. The purpose of this leaflet is to explain to you why you feel the way you do; what makes it happen; why it started happening in the first place; and most important of all what you can do about it to sort the problem out.

It's best to be honest right from the start. The treatment for agoraphobia and anxiety will involve a lot of effort and commitment from you. You will have to do difficult things. On the positive side though, if you do these things, if you put in the effort, the chances of success are really very good. In other words, if you do what is asked of you, it works!

This leaflet is intended to help you remember what your therapist has explained to you. You are not expected to remember it all in one go.

Read the leaflet carefully several times - the more you understand your problem the better.

1. ANXIETY

You will already have been told that anxiety is the cause of your difficulties. Most people who have not experienced the kind of problems you have would be amazed to discover just how strong and unpleasant the feelings of anxiety can be. That is not to say you are unusual though, there are a lot of people who have problems very similar to yourself. Anxiety based problems are some of the most common and yet least talked about difficulties there are. Most people who have these problems tend to keep them to

themselves. This can at times leave you feeling very alone and frightened. There are some very important things you should remember about anxiety:

Firstly, it is not an illness

Anxiety is not an illness, it is not a sign that there is anything wrong with your body or mind in any real way at all.

Anxiety is on occasion a perfectly natural and normal way to feel. All human beings feel anxious at some time or other, we all have good days and bad days. Not only is anxiety a normal way to feel, but there is a reason for being able to feel like this, anxiety has a purpose. Anxiety is as important a part of being a human being as having a heart that beats or lungs that breathe.

Secondly, it is not in your imagination

Anxiety is real, the physical feelings and sensations you get are really happening to you. Again, most people who have not felt anxiety at its strongest would be staggered to find out just how strong these feelings of anxiety are. Anxiety can effect you in many ways. It can effect you:

(a) Physically - with feelings like racing heart, dizziness, blurred vision, churning stomach, breathlessness, chest pains and tightness, wobbly legs and so on.

(b) Mentally - anxiety can effect the way you think. You may think `something awful will happen to me'. You may think you will lose control or collapse or have a heart attack, and you will watch out for signs of these things happening.

(c) Behaviour - anxiety effects what you do and how important it feels to do it. Anxiety often drives you to do things right away without hesitation. Very often it will also make you avoid doing things and avoid going places.

Thirdly, it is not dangerous

The feelings of anxiety will not hurt you in any way at all. Regardless of how strong these feelings are (and they really do feel that strong!) they will not cause you any harm at all.

To explain this better perhaps it would be best to explain what anxiety is. I have said it has a purpose and if that purpose is explained to you, you will be able to see why I can say it will not hurt you or harm you in any way.

2 WHAT IS ANXIETY?

Anxiety is your body's natural alarm system. It is the bit of your body that gets you ready to deal with danger. More than just warning you that danger is there, anxiety works to actually get you ready to deal with it. It peps up your body all at once so that you can be ready to either run or fight in a dangerous situation. This is called the `fight or flight' reaction.

The anxiety system works through the stress hormones, the best known of which is adrenaline. There is nothing subtle or sophisticated about the way it works, in fact it is very primitive. If you are in a dangerous situation adrenaline is passed into your blood and it travels around your body causing the physical effects you feel. These physical effects happen so that you can get out of danger, so that you can get out of trouble. They would not be able to do this if all they did was make you lose control, faint, have a heart attack or whatever. If these feelings did that to you then anxiety would be no use for the very job it is designed to do! All these feelings have a reason for happening and that reason is to get you out of trouble, not put you further in it.

Think how you would feel if you were walking down the road past a garden and a large dog suddenly bounced at the fence barking and snarling. You might feel your heart racing, sweating, or you may feel dizzy, stomach churning and so on. You might also find yourself thinking that a disaster will happen, such as the dog might get you, then anxiety would make you "think the worst". You might even run for a short distance. These are all things which happen when the anxiety system suddenly gets `switched on' all at once. The main thing here though is that once the danger is past, the feelings pass off. In other words, if the dog couldn't get through the fence you would walk on your way and all the strong feelings would gradually die away to nothing.

The adrenaline going into the bloodstream when the anxiety is switched on is rather like putting sugar into tea - you can put it in, but once it is in you can't take it back out again, but if you leave it, it dissolves away fairly quickly. In other words, if you leave these feelings of anxiety, even the strongest ones, they will die away and pass off without doing you any harm at all.

The explanation above refers to what happens in a real, dangerous situation. This raises some questions. Why are you feeling anxious in situations which you know are not dangerous, e.g. in busy shops or crowds? To explain this we need to look at how the problems of agoraphobia and anxiety develop in the first place.

3. HOW AGORAPHOBIA DEVELOPS

The way the problem develops obviously varies from person to person. There are some general rules though.

What usually happens is that someone who develops agoraphobia will have been under pressure for some time, often without realising it. This may have been because of a serious or sudden event such as the death of someone close or a serious illness. Or, it may have been due to other upsets or changes in their circumstances, e.g. losing a job, the break up of a marriage, moving to a new area or getting a new job. Problems can also develop after a long period of strain or worry or if the person has been depressed for a while.

What happens is that these strains and pressures cause the person to gradually become more anxious often without realising it. As their anxiety level goes up they become more irritable, have less patience and often find themselves much more easily wound up. When they are in this state the person's general level of anxiety is much higher than it was before and it takes really very little pressure for them to become so wound up that they experience very high levels of anxiety, or even panic.

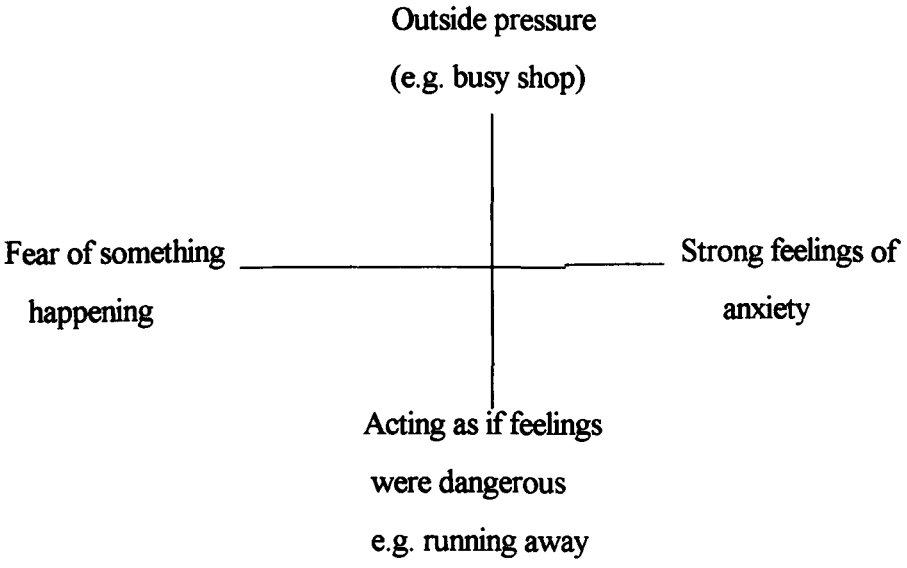
Why does this happen in shops or crowds? The answer is simple - we all feel a bit more aroused or worked up in crowds or busy places. How many people have you heard complaining about being frazzled or wound up after a busy afternoon's shopping, e.g. at Christmas time? The thing is, this increase in anxiety level is easy to cope with if you are generally feeling fairly calm. However, if you are generally tense and anxious this small increase in arousal can be enough to cause strong feelings of panic and anxiety. These feelings are very strong and unpleasant, they also seem unexpected and appear to come out of the blue. Looking back on it though you may be able to see where your problem started and that there is usually a fairly straightforward explanation for how they started. It may also be that the pressures that first started the problem have been sorted out now.

Why does the problem keep going? This is simply because anxiety is unpleasant enough to make the person worry about the feelings. This keeps their general level of anxiety fairly high so they continue to get strong feelings of anxiety in situations where they would only have felt a little aroused before.

Even though you may now understand how the problem started that doesn't change the fact that these feelings of anxiety are strong, unpleasant and frightening. Very often you are frightened that something awful will happen to you, that you might collapse, have a heart attack and so on. Not surprisingly, what people do is try to avoid this happening by running out of the place they are in and/or trying to control or fight off the feeling of fear and anxiety. Then the next time the person is in that place they are frightened they will feel anxious again -they start to feel frightened and because of this they leave the situation again. Over time the person begins to avoid a whole range of places and things, anything in fact which they feel might bring on the feelings. Unfortunately this only makes things worse. The old saying holds true here:

`Actions speak louder than words'

We have been told so far that these feelings won't hurt you. You may even know yourself that there is nothing really to be frightened of. That is why you may sometimes feel embarrassed about telling others about your problem. Even though you know in the back of your mind that nothing will happen to you, if you run away from the feelings or fight them you are still acting as if something dangerous will happen, and if you act as if something is dangerous then you will feel it is dangerous, and you will feel anxious and frightened. Your body's natural alarm system will get you ready to deal with this supposed danger by passing more adrenaline into the bloodstream, which causes more strong feelings, which in turn frightens you even more, so you try even more to avoid them. This builds up into a vicious circle which can be represented by the diagram on the next page:



So in fact someone who has agoraphobia is not frightened of shops or crowds or buses, they are frightened of the feelings that they get in shops or crowds or buses and these feelings are the physical feelings of fear and anxiety. The problem really is FEAR OF FEAR - you are frightened of being anxious and frightened.

This is a very difficult position to be in because the more anxious you feel the more you try to stop the feelings by fighting them off or leaving the situation, and the more you are acting as if they really are dangerous, which makes you feel more anxious in turn.

The problem is this - you have been told that the feelings are not dangerous. Avoiding them or trying to fight them off only makes them worse, so how do you prove to yourself that these feelings are not dangerous when they feel so strong and convincing when they are there?

4 HOW TO DEAL WITH THE PROBLEM - GETTING RID OF AGORAPHOBIA

The solution is easy to explain, but harder to do.

It is the feelings that you are frightened of, so how do you prove to yourself that there is really nothing to be afraid of in these feelings? Simple - you let them be there, you don't try and avoid them, you just let them happen, let them pass off, without acting as if they are dangerous in any way at all.

For you to be able to do this, the feelings are obviously going to have to be there in the first place. In other words, you are going to have to feel anxious to get over this problem.

This is not really so bad, though - all right so you have to feel anxious so that you can practise not running away and not trying to fight it off, so you can practise being in control and letting the feelings run their course. To do this the feelings have to be there. Really the feelings have been there until now anyway, except this time they are going to be there for a reason, which is so that you can get better and control the problem. What you have to do then is deliberately set out to feel anxious.

The easiest way for you to get the feelings to be there is to go back and try doing all the things you have been avoiding up until now. If you have been avoiding going to the shops, now you go. If you haven't been on a bus for a while, now is the time to try. You must get back to doing all the things you have stopped doing as quickly as possible. You must also expect to feel anxious when you do this at first - that is good - the whole point of the treatment is for you to practise not acting as if you are frightened of the feelings and letting them pass off in their own time. Gradually, over time, the more you do this the less the feelings will happen.

How do you deal with the feelings of anxiety when they happen?

When you go back to a place you've been avoiding and you start to feel anxious, DON'T TRY TO RUN AWAY OR FIGHT OFF THE FEELINGS - follow these rules.

Rules for coping with panic

i) The best advice you can ever be given is to let the anxiety and panic happen keep going and wait until it passes.

ii) Remember these are natural normal feelings

- they are not dangerous
- they will not hurt you
- they will pass in their own time if you let them.

They may be unpleasant, BUT THAT IS ALL THEY ARE.

It sounds strange, but just relax and let yourself feel anxious. You must accept that the feelings are happening, say to yourself "all right so I'm feeling anxious but I'm not going

to let it stop me doing anything and I'll control these feelings instead of the feelings controlling me. These feelings are not going to push me around".

iii) Do not act as if the feelings are dangerous in any way at all. Don't act frightened, don't run away, stay where you are. Don't rush to get the shopping finished faster so you can get out of the shop sooner. Don't tense up and do try to see the feelings through, just relax and let them happen. Deliberately act calm, even though you will not feel calm to begin with.

If the anxiety makes you feel as if you must do something to stop a disaster - DO THE OPPOSITE. For example, if you feel as if you must hold on to something to avoid falling over, deliberately walk away from hand holds. Or, if you feel you have to walk closer to the shelves in the supermarket because it makes you feel more comfortable -then walk down the middle of the aisles. Remember, you are in control, you are in charge.

So you will have to think quite carefully about all what things you do when you feel anxious or panicky and decide " .. am I doing this to try and fight off the anxiety or avoid a disaster ?" - if so, this is something you will have to change so you are doing the opposite of what the anxiety says to do.

There will be many of these important little tricks which you have to learn. Many of them will be particular to your own problem. Try out your alternative actions and remember the golden rule, DON'T ACT FRIGHTENED OF THE FEELINGS. Don't let them push you into doing things just carry on and act as if they weren't there - you rule them, don't let them rule you, you control them by not giving in to them.

iv) The most important thing of all to remember is NEVER LEAVE A SITUATION UNTIL THE FEAR OR PANIC HAS STARTED TO GO DOWN.

v) Regard each time you feel anxious or each panic attack as an opportunity to practise not acting frightened of these feelings, an opportunity to practise coping with the feelings. The more you practise the better you learn to cope and gradually the less the feelings will happen.

You will have realised by now that you have quite a bit of work ahead of you, even though the task will seem daunting at first you don't have to keep following these rules for ever, just until your anxiety fades and the problem is sorted out. Just now, you shouldn't avoid any situation that makes you feel anxious, then once the problem is sorted out you will be free from it and you can go back to living your life however you please.

For the moment though you have a lot of practising to do. To make this easier for yourself think about what you have to do and organise and plan it as much as possible. You can write down your plans too - to make them more definite.

5 HOW TO PLAN YOUR PRACTICE

The first thing here is that planning your practice is not half as important as doing it! However, there are some things which can help you get back to doing all the things you used to avoid.

i) Draw up a list of targets, and be specific. Don't just say "I'll go to the shops sometime", be definite, e.g. "I'll go to Fine Fare tomorrow and spend at least an hour shopping".

Once you have drawn up this list try and tackle the most difficult target you feel you can manage to begin with. After you have practised this a lot work your way up the list tackling the more difficult targets.

ii) The time you spend in a situation is vital. Fifteen minutes is just not enough - that would be like dipping your toe in a swimming pool and then saying you'd learned to swim. You must stay in the situation until the anxiety begins to pass off. More than this though -the longer you stay the better. Plan to stay in a situation for at least one hour if possible. If you can get yourself out for 1-2 hours a day or more, this would be excellent.

iii) How often you practise is vital too - once a week would be no use. Plan to go out every day. The rule is quite simply, `PRACTICE MAKES PERFECT'. The more you practise the quicker you get over the problem.

iv) Once is not enough - after you have tried something once -don't just leave it and think `that's it sorted now' -IT'S NOT: practise things again and again until you really feel

you've mastered them. Keep going until you can really believe there is no danger there now.

v) 'You've got to be cruel to be kind' - don't let yourself take it too easy. You've got to push yourself a bit. You decide what targets you have to face, you take charge of your treatment. This is the best possible thing to do because if you decide to do something you used to be frightened of then just by deciding like that you have already stopped being so frightened of it.

vi) 'Don't put off until tomorrow what you can do today'. Try to do things as soon after you have decided on them as possible. Don't try and plan things weeks ahead. If you have a big target too far ahead you give yourself too much time to worry about it - it gets blown up out of proportion. Forget about the future, take things A DAY AT A TIME, a step at a time. Do things NOW not in the distant future.

vii) Try not to rely on other people, try to do things as much as you can yourself. (That's not to say you can't discuss it with other people though! In fact it is helpful if someone else knows what you are doing and is supportive).

viii) Don't cheat! Be honest with yourself. If you don't want to do something because you are afraid, admit it, accept it and plan to tackle it as soon as possible. Remember - if you cheat the only person you're cheating is yourself.

6 POINTS TO NOTE

To finish with here are some points to bear in mind while you are practising:

- It takes time - the problem didn't develop overnight and it has been there for a while, so don't expect it to disappear overnight either. It usually takes months not weeks to fully get over this kind of problem, but remember the more you work at it the quicker it goes.

- Things may be a bit worse before they get better. Sometimes (but not always) people can find themselves feeling a bit more anxious when they first start practising. This is simply because they have started back doing a lot of things they had been avoiding doing for a while. If this happens to you, don't worry about it - it's perfectly normal and it usually passes fairly quickly. It is not a sign that you're failing or getting it wrong.

- It is tiring - when you have gone through a panic and let the feelings pass you will feel tired. This is perfectly natural - being anxious is hard physical work so of course you will feel tired afterwards. Don't worry about this.

- You may get occasional setbacks on the road to recovery. This is normal. Remember at the start of this leaflet I said that we all have good days and bad days. If once you start to feel better and you have a set back and perhaps have another panic attack, don't worry about it. You have <u>not</u> gone back to square one. Just deal with it the way you have been practising and keep going. This kind of anxiety based problem does not disappear all at once. What happens when you get better is you begin to have less anxiety less often - still with bad days in between but gradually the good days begin to outnumber the bad days until finally you realise that its been a while since you have had any really bad days.

- There are some things which can affect you physically and make you more likely to feel anxious - try to avoid these if possible.

- Too much tea or coffee - if you drink a lot of coffee try switching to a decaffeinated brand.
Also too many cigarettes have a similar effect. Try to avoid smoking in excess.

- Too much alcohol - or to be specific, bad hangovers make you much more likely to feel anxious. Try and avoid these.

- Too little food - if you are hungry, if you are missing meals you will feel more anxious. Eat sensible, regular meals.

- Too little rest - being overtired and overworked means you are more likely to feel anxious. This treatment is definitely hard work so make sure you get the opportunity to rest and relax for a little while each day.

- Finally, not enough relaxation. You are going to be doing something which is hard, tiring and demanding. Try to make sure that you get some time for yourself to do the things you enjoy doing. If you work hard, treat yourself.

Read this leaflet carefully, several times. Make sure you understand what you have to do. THEN - its up to you - remember, work hard at it, do your best, no-one can ask for more than that.

APPENDIX II **MEASURES**

DSM III-R Checklist

Patient Initials: [ ] [ ] [ ] Date: [ ] [ ] [ ]

DSM III-R CRITERIA FOR PANIC DISORDER
(with or without agoraphobia)

	Present	Absent
A. PANIC DISORDER One or more discrete periods of intense fear or discomfort have occurred that were (1) unexpected and (2) not triggered by situations in which the person was the focus of others' attention.	1	2
B. ONE OR MORE PANIC ATTACKS		
1. Four attacks, as defined in criterion A, have occurred within a four-week period.	1	2
2. One or more attacks have been followed by a period of at least a month of persistent fear of having another attack.	1	2
C. FEATURES OF PANIC DISORDER At least **four** of the following symptoms must have developed during at least one of the attacks:		
1. shortness of breath (dyspnea) or smothering sensations	1	2
2. dizziness, unsteady feelings, or faintness	1	2
3. palpitations or accelerated heart rate (tachycardia)	1	2
4. trembling or shaking	1	2
5. sweating	1	2
6. choking	1	2
7. nausea or abdominal distress	1	2
8. depersonalization or derealization	1	2
9. numbness or tingling sensations (paresthesias)	1	2
10. flushes (hot flashes) or chills	1	2
11. chest pain or discomfort	1	2
12. fear of dying	1	2
13. fear of going crazy or doing something uncontrolled	1	2

	Yes	No
D. ONSET OF ATTACKS During some of the attacks: four or more of the C symptoms — developed suddenly — increased in intensity within ten minutes of the beginning of the first C symptom	1	2
E. ORGANIC FACTORS (must be ruled out) The disorder was initiated and maintained by an organic factor, such as amphetamine or caffeine intoxication or hyperthyroidism.	1	2

F. TYPES OF PANIC DISORDER

0. Without Agoraphobia [ ]
2. With Agoraphobia: If present, rate severity:
   - 2. Mild: some avoidance
   - 3. Moderate: constricted life-style
   - 4. Severe: nearly housebound or unable to leave the house unaccompanied.

   [ ]
   - 1. in partial remission: some avoidance during past six months
   - 0. in full remission: no avoidance during past six months

   [ ]

G. SEVERITY OF PANIC ATTACKS during the past month:

1. mild: either all have been limited symptom attacks or there has been no more than one attack [ ]
2. moderate: between mild and severe
3. severe: at least eight attacks

Investigators signature .....

Hamilton Anxiety Scale (HAM-A)

Patient Initials: _____ Date: ___ ___ ___

HAMILTON RATING SCALE FOR ANXIETY

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
1.	ANXIOUS MOOD Worries, anticipation of the worst, fearful anticipation, irritability					
2.	TENSION Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax					
3.	FEARS Of dark, of strangers, of being left alone, of animals, of traffic, of crowds					
4.	INSOMNIA Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors					
5.	INTELLECTUAL Difficulty in concentration poor memory					
6.	DEPRESSED MOOD Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing					
7.	SOMATIC (Muscular) Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone					
8.	SOMATIC (Sensory) Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation					

Patient Initials: [ ]

HAMILTON RATING SCALE FOR ANXIETY – *continued*

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

TOTAL [ ]

N.B.: PATIENT MUST SCORE 15 OR MORE TO BE ELIGIBLE FOR THE STUDY

Investigators signature .....

Symptom Rating Test (SRT)

Patient No: _____

Date: _____ Patient Initials: _____

KELLNER/SHEFFIELD SELF RATING SCALE

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				

Please turn over . . .

Patient No: _____

Patient Initials: _____

	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				

Montgomery Asberg Depression Rating Scale (MADRS)

Patient Initials: Date:

MADRS SCALE

Please record severity of symptoms in the box on the right hand side.

ITEM No.	SYMPTOM		SCORE
1	**Apparent Sadness** Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.		
	No sadness.	0 1	
	Looks dispirited but does brighten up without difficulty	2 3	
	Appears sad and unhappy most of the time.	4 5	
	Looks miserable all the time. Extremely despondent.	6	
2	**Reported Sadness** Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.		
	Occasional sadness in keeping with the circumstances	0 1	
	Sad or low but brightens up without difficulty.	2 3	
	Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.	4 5	
	Continuous or unvarying sadness, misery or despondency.	6	
3	**Inner Tension** Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.		
	Placid. Only fleeting inner tension.	0 1	
	Occasional feelings of edginess and ill-defined discomfort.	2 3	
	Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.	4 5	
	Unrelenting dread or anguish. Overwhelming panic.	6	
4	**Reduced Sleep** Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.		
	Sleeps as usual.	0 1	
	Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.	2 3	
	Sleep reduced or broken by at least two hours.	4 5	
	Less than two or three hours sleep.	6	
5	**Reduced Appetite** Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.		
	Normal or increased appetite.	0 1	
	Slightly reduced appetite.	2 3	
	No appetite. Food is tasteless.	4 5	
	Needs persuasion to eat at all.	6	

Patient Initials: ☐

MADRS SCALE – *continued*

ITEM No.	SYMPTOM		SCORE
6	**Concentration difficulties** Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.		
	No difficulties in concentrating	0 1	
	Occasional difficulties in collecting one's thoughts.	2 3	
	Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation	4 5	☐
	Unable to read or converse without great difficulty	6	
7	**Lassitude** Representing a difficulty getting started or slowness initiating and performing everyday activities.		
	Hardly any difficulty in getting started. No sluggishness.	0 1	
	Difficulties in starting activities.	2 3	
	Difficulties in starting simple routine activities which are carried out with effort.	4 5	☐
	Complete lassitude. Unable to do anything without help.	6	
8	**Inability to Feel** Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.		
	Normal interest in the surroundings and in other people.	0 1	
	Reduced ability to enjoy usual interests.	2 3	
	Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.	4 5	
	The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.	6	☐
9	**Pessimistic thoughts** Representing thoughts of guilt, inferiority, self-approach, sinfulness, remorse and ruin.		
	No pessimistic thoughts.	0 1	
	Fluctuating ideas of failure, self-reproach or self-depreciation.	2 3	
	Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.	4 5	
	Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.	6	☐
10	**Suicidal thoughts** Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.		
	Enjoys life or takes it as it comes.	0 1	
	Weary of life. Only fleeting suicidal thoughts.	2 3	
	Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.	4 5	
	Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	6	☐
		TOTAL	☐

N.B.: PATIENTS SCORING 21 OR MORE MUST BE EXCLUDED FROM THE STUDY

Investigators signature .....

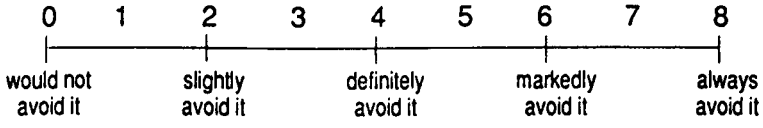
Fear Questionnaire (FQ)

Patient No: ☐

Date: ☐☐☐☐☐☐ Patient Initials: ☐☐☐

FQ

Choose a number from the scale below to show how much you would avoid each of the situations listed below because of fear or other unpleasant feelings. Then write the number you choose in the box opposite each situation.



1. Main phobia you want treated (describe in your own words) ..... ☐
2. Injections or minor surgery ☐
3. Eating or drinking with other people ☐
4. Hospitals ☐
5. Travelling alone by bus or coach ☐
6. Walking alone in busy streets ☐
7. Being watched or stared at ☐
8. Going into crowded shops ☐
9. Talking to people in authority ☐
10. Sight of blood ☐
11. Being criticised ☐
12. Going alone far from home ☐
13. Thought of injury or illness ☐
14. Speaking or acting to an audience ☐
15. Large open spaces ☐

Please turn over

Patient No: ☐

Patient Initials: ☐

FQ(2)

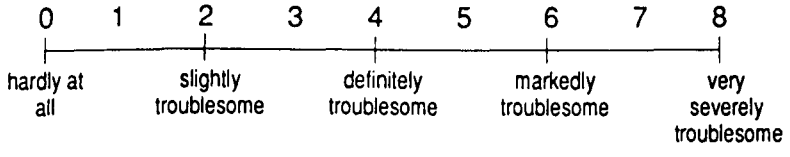
16. Going to the dentist ☐

17. Other situations (describe) ..... ☐

.....

leave blank ☐ Ag (5,6,8,12,15) + ☐ BI (2,4,10,13,16) + ☐ Soc (3,7,9,11,14) Total: ☐

Now choose a number from the scale below to show how much you are troubled by each problem listed and write the number in the box opposite



18. Feeling miserable or depressed ☐

19. Feeling irritable or angry ☐

20. Feeling tense or panicky ☐

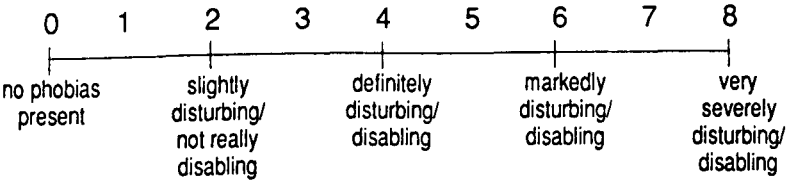
21. Upsetting thoughts coming into your mind ☐

22. Feeling you or your surroundings are strange and unreal ☐

23. Other feelings (describe)..... ☐

Total ☐

How would you rate the present state of your phobic symptoms on the scale below?



Please write one number between 0 and 8 ☐

Panic Attack Diary

Patient No

Patient Initials

PANIC DIARY

Diary No _____ Group No. _____

Doctor / Health Centre .....

.....

IT IS IMPORTANT THAT YOU COMPLETE THIS DIARY OF PANIC ATTACKS EXPERIENCED EVERY DAY

PLEASE REMEMBER TO BRING THIS DIARY TO YOUR NEXT APPOINTMENT

.....

YOUR NEXT APPOINTMENT IS .....

PLEASE COMPLETE THIS DIARY FOR THE 7 DAYS

STARTING ..... AND FINISHING .....

PANIC DIARY - INSTRUCTIONS

This diary is for you to note down any panic attacks you might have. Each day note down the day and the date.

If you do not have a panic attack that day - tick the 'NO' box. If you do have a panic attack, tick the 'YES' box and fill in the diary following these instructions :

A panic attack is a sudden build-up of fear and anxiety along with unpleasant physical feelings. If a panic occurs, note it down in the first column in the form COLUMN A. If you have another panic attack that day, note it in COLUMN B, and so on.

First, rate how SEVERE the attack is on this 0 - 10 scale :-

0	1	2	3	4	5	6	7	8	9	10
Not at all severe		Mild			Moderate			Marked		Extreme worst it could be

Then, note down how long the panic lasted (hours / minutes) in the PANIC DURATION box.

Then, go down the list of physical symptoms and put a tick (✓) next to the ones that you felt during the panic attack.

If another panic attack happens that day, follow these instructions again for COLUMN B.

In the section marked 'SITUATIONS', note down only briefly where you were and what you were doing

DAY ..... DATE .....

PANIC ATTACKS YES ☐ NO ☐

SITUATION - Where panic happened

	A	B	C	D	E
Severity of attack (0 -10)					
Panic Duration (mins)					
Symptoms experienced (tick boxes below)					
Breathlessness					
Dizzyness/feeling faint					
Palpitations or racing heart					
Trembling/shaking					
Sweating					
Choking					
Nausea					
Unreal feelings/ detachment					
Numbness or tingling sensations					
Hot or cold flushes					
Chest pain or discomfort					
Fear of dying					
Fear of losing control					
Other					

DAY ..... DATE .....

PANIC ATTACKS YES [ ] NO [ ]

SITUATION - Where panic happened

	A	B	C	D	E
Severity of attack (0 -10)					
Panic Duration (mins)					
Symptoms experienced (tick boxes below)					
Breathlessness					
Dizzyness/feeling faint					
Palpitations or racing heart					
Trembling/shaking					
Sweating					
Choking					
Nausea					
Unreal feelings/ detachment					
Numbness or tingling sensations					
Hot or cold flushes					
Chest pain or discomfort					
Fear of dying					
Fear of losing control					
Other					

Global Severity of Illness/ Change in Symptoms

Patient No: Date:

CLINICAL GLOBAL IMPRESSION SCALE

Considering your total clinical experience of this condition, how emotionally distressed is the patient NOW?

1 = Normal
2 = Borderline
3 = Mild
4 = Moderate
5 = Marked
6 = Severe
7 = Extreme

Please enter score in box

CLINICAL GLOBAL IMPROVEMENT

Compared to his/her condition ON ENTRY to the study, how much has the patient changed?

1 = very much improved
2 = much improved
3 = minimally improved
4 = no change
5 = minimally worse
6 = much worse
7 = very much worse

Please enter score in box

Investigators signature .....

General Health Questionnaire (GHQ)

Patient No: ____

Date: ____ Patient Initials: ____

GENERAL HEALTH QUESTIONNAIRE

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 too tired and exhausted even to eat?	Not at all	No more than usual	Rather more than usual	Much more than usual

Please turn over . . .

Patient No:

GENERAL HEALTH QUESTIONNAIRE (2)

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.	–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 satis-fied 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

Patient No:

GENERAL HEALTH QUESTIONNAIRE (3)

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.	–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 unhapy 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

Please turn over . . .

Patient No:

GENERAL HEALTH QUESTIONNAIRE (4)

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.	–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 your mind?	Definitely not	I don't think so	Has crossed my mind	Definitely has

Sheehan Disability Scale (SD)

Patient No:

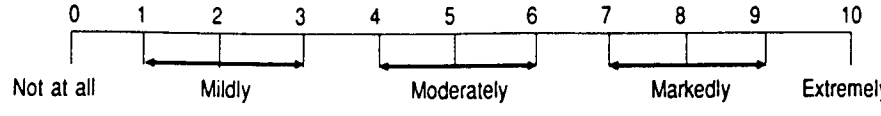
Date:

Patient Initials:

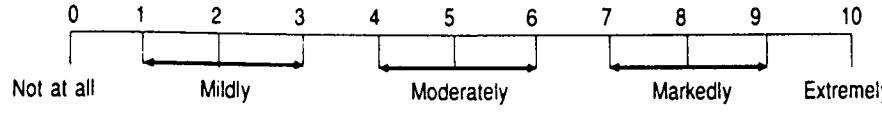
SHEEHAN SCALE

Instructions: For each scale, circle only **one** number which best describes your situation now.

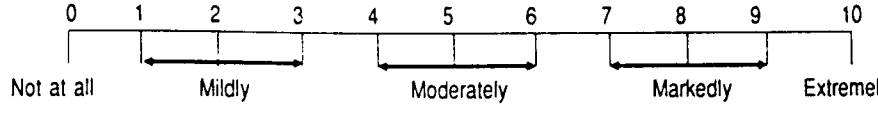
1. Work — The symptoms have disrupted your work:



2. Social Life — The symptoms have disrupted your social/leisure activities:



3. Family Life/Home Responsibilities — The symptoms have disrupted your family life:



Anxiety Sensitivity Index (ASI)

Patient No: _____

Patient Initials: _____ Date: ___ ___ ___

ASI

Answer the following questions by ticking (✔) the appropriate box.
Tick one box for each question.

	0 very little	1 a little	2 some	3 much	4 very much
It is important to me not to appear nervous					
When I cannot keep my mind on a task, I worry that I might be going crazy					
It scares me when I feel 'shaky' (trembling)					
It scares me when I feel faint					
It is important to me to stay in control of my emotions					
It scares me when my heart beats rapidly					
It embarrasses me when my stomach growls					
It scares me when I am nauseous					
When I notice that my heart is beating rapidly, I worry that I might have a heart attack					
It scares me when I become short of breath					
When my stomach is upset, I worry that I might be seriously ill					
It scares me when I am unable to keep my mind on a task					
Other people notice when I feel shaky					
Unusual body sensations scare me					
When I am nervous, I worry that I might be mentally ill					
It scares me when I am nervous					

Eysenck Personality Questionnaire (EPQ)

EPQ

Patient No: _____

Date: | | | | Patient Initials: _____

INSTRUCTIONS Please answer each question by putting a circle around the "YES" or the "NO" following the question. There are no right or wrong answers, and no trick questions. Work quickly and do not think too long about the exact meaning of the questions.

PLEASE REMEMBER TO ANSWER EACH QUESTION

1	Do you have many different hobbies?	YES	NO
2	Do you stop to think things over before doing anything?	YES	NO
3	Does your mood often go up and down?	YES	NO
4	Have you ever taken the praise for something you knew someone else had really done?	YES	NO
5	Are you a talkative person?	YES	NO
6	Would being in debt worry you?	YES	NO
7	Do you ever feel "just miserable" for no reason?	YES	NO
8	Were you ever greedy by helping yourself to more than your share of anything?	YES	NO
9	Do you lock up your house carefully at night?	YES	NO
10	Are you rather lively?	YES	NO
11	Would it upset you a lot to see a child or an animal suffer?	YES	NO
12	Do you often worry about things you should have done or said?	YES	NO
13	If you say you will do something, do you always keep your promise no matter how inconvenient it might be?	YES	NO
14	Can you usually let yourself go and enjoy yourself at a lively party?	YES	NO
15	Are you an irritable person?	YES	NO
16	Have you ever blamed someone for doing something you knew was really your fault?	YES	NO
17	Do you enjoy meeting new people?	YES	NO
18	Do you believe insurance schemes are a good idea?	YES	NO
19	Are your feelings easily hurt?	YES	NO
20	Are *all* your habits good and desirable ones?	YES	NO

Please turn over . . .

EPQ(2)

Patient Initials: _____

21	Do you tend to keep in the background on social occasions?	YES	NO
22	Would you take drugs which may have strange or dangerous effects?	YES	NO
23	Do you often feel "fed-up"?	YES	NO
24	Have you ever taken anything (even a pin or button) that belonged to someone else?	YES	NO
25	Do you like going out a lot?	YES	NO
26	Do you enjoy hurting people you love?	YES	NO
27	Are you often troubled about feelings of guilt?	YES	NO
28	Do you sometimes talk about things you know nothing about?	YES	NO
29	Do you prefer reading to meeting people?	YES	NO
30	Do you have enemies who want to harm you?	YES	NO
31	Would you call yourself a nervous person?	YES	NO
32	Do you have many friends?	YES	NO
33	Do you enjoy practical jokes that can sometimes really hurt people?	YES	NO
34	Are you a worrier?	YES	NO
35	As a child did you do as you were told immediately and without grumbling?	YES	NO
36	Would you call yourself happy-go-lucky?	YES	NO
37	Do good manners and cleanliness matter much to you?	YES	NO
38	Do you worry about awful things that might happen?	YES	NO
39	Have you ever broken or lost something belonging to someone else?	YES	NO
40	Do you usually take the initiative in making new friends?	YES	NO
41	Would you call yourself tense or "highly-strung"?	YES	NO
42	Are you mostly quiet when you are with other people?	YES	NO
43	Do you think marriage is old-fashioned and should be done away with?	YES	NO
44	Do you sometimes boast a little?	YES	NO
45	Can you easily get some life into a rather dull party?	YES	NO
46	Do people who drive carefully annoy you?	YES	NO
47	Do you worry about your health?	YES	NO
48	Have you ever said anything bad or nasty about anyone?	YES	NO
49	Do you like telling jokes and funny stories to your friends?	YES	NO
50	Do most things taste the same to you?	YES	NO
51	As a child were you ever cheeky to your parents?	YES	NO
52	Do you like mixing with people?	YES	NO
53	Does it worry you if you know there are mistakes in your work?	YES	NO
54	Do you suffer from sleeplessness?	YES	NO

EPQ(3)

Patient Initials: _____

55	Do you always wash before a meal?	YES	NO
56	Do you nearly always have a "ready answer" when people talk to you?	YES	NO
57	Do you like to arrive at appointments in plenty of time?	YES	NO
58	Have you often felt listless and tired for no reason?	YES	NO
59	Have you ever cheated at a game?	YES	NO
60	Do you like doing things in which you have to act quickly?	YES	NO
61	Is (or was) your mother a good woman?	YES	NO
62	Do you often feel life is very dull?	YES	NO
63	Have you ever taken advantage of someone?	YES	NO
64	Do you often take on more activities than you have time for?	YES	NO
65	Are there several people who keep trying to avoid you?	YES	NO
66	Do you worry a lot about your looks?	YES	NO
67	Do you think people spend too much time safeguarding their future with savings and insurances?	YES	NO
68	Have you ever wished that you were dead?	YES	NO
69	Would you dodge paying taxes if you were sure you could never be found out?	YES	NO
70	Can you get a party going?	YES	NO
71	Do you try not to be rude to people?	YES	NO
72	Do you worry too long after an embarrassing experience?	YES	NO
73	Have you ever insisted on having your own way?	YES	NO
74	When you catch a train do you often arrive at the last minute?	YES	NO
75	Do you suffer from "nerves"?	YES	NO
76	Do your friendships break up easily without it being your fault?	YES	NO
77	Do you often feel lonely?	YES	NO
78	Do you always practice what you preach?	YES	NO
79	Do you sometimes like teasing animals?	YES	NO
80	Are you easily hurt when people find fault with you or the work you do?	YES	NO
81	Have you ever been late for an appointment or work?	YES	NO
82	Do you like plenty of bustle and excitement around you?	YES	NO
83	Would you like other people to be afraid of you?	YES	NO
84	Are you sometimes bubbling over with energy and sometimes very sluggish?	YES	NO
85	Do you sometimes put off until tomorrow what you ought to do today?	YES	NO
86	Do other people think of you as being very lively?	YES	NO
87	Do other people tell you a lot of lies?	YES	NO
88	Are you touchy about some things?	YES	NO
89	Are you always willing to admit it when you have made a mistake?	YES	NO
90	Would you feel very sorry for an animal caught in a trap?	YES	NO

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL THE QUESTIONS

Social Maladjustment Questionnaire (SocMal)

Patient No: ____

Date: ____ Patient Initials: ____

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 OUTISDE 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 . . . .

Patient Initials:

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? (including 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/ cohabitating	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

Patient Initials:

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 . . . .

Patient Initials: [ ]

SOCIAL QUESTIONNAIRE (4)

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 .....

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APPENDIX III GLOSSARY FOR USE WITH THE HAMILTON ANXIETY SCALE (POWER ET AL 1983)

ASSESSMENT OF ANXIETY STATES

GLOSSARY FOR USE WITH THE HAMILTON ANXIETY SCALE

K.G. Power
Clinical Psychologist
University of Stirling
Stirling

M.J. Mitchell
Clinical Scientist
Astra Clinical Research Unit
10 York Place
Edinburgh

D.W.A. Jerrom
Principal Clinical Psychologist
and Clinical Research Fellow
University of Stirling
Stirling

October 1983

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) Development of frigidity)	in females alone
Ejaculatio praecox) Loss of erection) Impotence)	in males alone

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.