

Anxiety Disorders and their Treatment
A Critical Review of the Evidence-Based Literature

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PREFACE

Anxiety disorders are among the most common mental health problems. According to the Mental Health Supplement of the 1990 Ontario Health Survey, 9% of men and 16% of women experienced anxiety in the twelve months preceding the survey. A 1984 study of psychiatric disorders in Edmonton, Canada reported a lifetime prevalence rate of 11.2% for any anxiety/somatoform disorder. These disorders are often associated with other psychiatric problems, including depression and substance abuse. Anxiety disorders carry substantial personal, socio-economic and societal costs in terms of lost wages, decreased productivity, reduced quality of life, and frequent utilization of health care services.

Effective pharmacological, psychotherapeutic (cognitive-behavioural therapy), and behavioural interventions exist to treat the anxiety disorders. Recent empirical evidence, however, suggests a lack of knowledge among health and mental health professionals of effective treatments for these disorders, and use of treatments which are often not based on empirical research.

To contribute to the empirical knowledge base of effective treatment strategies for anxiety disorders, and to further discussions on these issues among stakeholders in the mental health field, a critical review of the evidence-based treatment literature was commissioned by the Health Promotion and Programs Branch of Health Canada. A discussion paper, based on the findings of the review, was also prepared, and is available under separate cover. Both reports were prepared by Martin Antony, Ph.D, and Richard Swinson, M.D., at the Clarke Institute of Psychiatry in Toronto, Ontario. The commitment of the authors to ensure the accuracy and completeness of the reports is much appreciated.

The review should be of interest to both health and mental health researchers and to anyone involved in the treatment of anxiety disorders. The review and the discussion paper could provide a basis for possible collaborative activities among stakeholders to address the treatment issues identified in the literature.

EXECUTIVE SUMMARY

This report critically reviews the current state of knowledge regarding the effectiveness of various approaches used to treat the six main types of anxiety disorders. A companion discussion paper entitled “Anxiety Disorders: Future Directions for Research and Treatment” summarizes the findings of treatment studies cited in this paper and suggests implications for future research, quality of care, and (health) professional and public education.

Computer literature searches of the Medline and PsychLit data bases were conducted for articles on the treatment of anxiety disorders published within the past 15 years (1981 to 1996). The key words used were combinations of each disorder name and the word “treatment” (e.g., treatment and panic disorder). In addition, a manual literature search was conducted by scanning the reference sections of recent review papers and treatment studies.

Studies were required to meet a number of author-defined criteria to be included in this review: controlled research studies (involving control or comparison groups); a minimum of ten participants per group; and use of diagnostic criteria from DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition)(American Psychiatric Association, 1980) or later. Studies of mixed groups of patients (e.g., panic disorder and generalized anxiety disorder) were not included unless it was possible to separate out the effects of treatment on each disorder.

On the basis of these criteria, pharmacotherapeutic studies and studies employing cognitive and behavioural approaches were included for review. Meta-analytic studies were also reviewed when available. Studies of self-help (self-instruction) treatments (e.g., self-help books) and treatments involving minimal therapist contact (e.g., treatment by telephone) were also included where available. However, studies of the effectiveness of (participation in) self-help groups did not meet the criteria and were not included. Studies of other forms of psychotherapeutic interventions (e.g., psychodynamic and humanistic approaches) were

not included as they did not meet the above criteria. In total, over 200 treatment studies were excluded from this review.

The studies cited in this review represent the existing “state of the art” research in the area of treatment of the anxiety disorders. Nonetheless, the authors identify a number of methodological limitations in this literature, including: *possible inadequacy of treatment delivery within studies; inconsistency in measurement or reporting of treatment compliance and treatment integrity; use of limited outcome measures* (which focus on symptom measurement only, at the expense of functional impairment, quality of life, and other dimensions related to the impact of the disorder on the individual, despite the fact that diagnoses of anxiety disorders involve significant impact on daily functioning); *inconsistency between studies in the types of outcome measures used; and inconsistency between studies in the types of assessment (measurement) instruments used.* The authors also note that the quality of research varies greatly across the anxiety disorders, with, for example, the state of the research being quite advanced for panic disorder. In contrast, the other anxiety disorders have not been studied as thoroughly, and existing studies suffer from a number of methodological flaws (e.g., inappropriate diagnostic criteria) which limit their usefulness.

The Anxiety Disorders

The anxiety disorders are a group of psychological problems whose key features include excessive anxiety, fear, worry, avoidance, and compulsive rituals. The most prevalent anxiety disorders listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994) include: *panic disorder with and without agoraphobia (PDA and PD); obsessive-compulsive disorder (OCD); social phobia; generalized anxiety disorder (GAD); specific phobia; and posttraumatic stress disorder (PTSD).* The diagnostic criteria for these disorders are included in Appendix 2. Acute stress disorder, a variant of PTSD with a briefer duration, agoraphobia without a history of panic disorder, and anxiety disorders induced by a general medical condition or a substance are not

discussed, due to the lack of research on specific strategies for dealing with these conditions. Finally, anxiety disorders classified as “not otherwise specified” are not discussed in this review due to the heterogeneity of this category and the lack of studies describing individuals who receive this diagnosis.

Prevalence, Comorbidity, Risk Factors, and Etiology

Most of the anxiety disorders are more common among women than men. A recent study reported a one-year *prevalence rate* for anxiety disorders in Ontario (Canada) of 9% for men and 16% for women. Lifetime prevalence rates, reported in North American epidemiological research, for experiencing any anxiety disorder range from 10.4% to 25.1%. The lifetime prevalence rates for specific anxiety disorders range from 3.5% for panic disorder to 13.3% for social phobia in recent epidemiological research (see Appendix 1 for data on specific types of anxiety disorders and for an explanatory note on the variations in prevalence rates).

Most individuals with anxiety disorders do not present with a single disorder. Common *comorbid conditions* include another anxiety disorder, depressive mood disorder (i.e., major depression or dysthymic disorder), alcohol and substance abuse, and personality disorders.

A number of *risk factors* and socio-demographic variables have been identified for these disorders and include severe abuse, parental mental disorder, parental behaviour (e.g., a tendency to be overprotective), and family history of anxiety. On average, many of the anxiety disorders tend to first develop when individuals are in their twenties, although there is much variation across the various disorders with respect to the range of ages at which the disorders begin. Risk factors for developing specific types of anxiety disorders have also been identified. These include perceived stressful life events (for PDA and PD), childhood history of separation (for social phobia), anxiety in childhood (for GAD), being female (for specific phobia, PDA and GAD), and traumatic events (for both specific phobia and PTSD). Not all individuals who experience these risk factors develop anxiety

disorders. The role of mediating variables, such as social support or biological predispositions, is under investigation.

Theories of the *etiology of anxiety disorders* are derived from a broad range of perspectives, from psychodynamic perspectives to evolutionary models. The most influential theoretical models for the anxiety disorders have come from two broad perspectives: cognitive-behavioural and biological.

Although cognitive and behavioural models of anxiety are often grouped together, the proponents of each perspective tend to emphasize different variables in their theories. Behavioural theorists tend to focus on learning experiences involving classical and operant conditioning that lead to the development and maintenance of fear. By contrast, cognitive theorists emphasize the importance of beliefs, predictions, interpretations, and cognitive biases in the development and maintenance of disorders.

For the most part, biological models of anxiety disorders have focused on particular neurotransmitter systems, such as the noradrenergic system (for PD), the serotonergic system (for OCD), and the GABA-benzodiazepine system (for GAD). For social phobia, some researchers have suggested that dopamine may be most relevant. Of course it is likely that a variety of neurotransmitters acting across different areas of the brain are involved in the etiology and maintenance of anxiety and fear.

Health Care Utilization and Economic Costs

Research suggests that individuals with anxiety disorders have more frequent contact with the health care system than does the general population. These individuals tend to seek help from the general health care system, as opposed to the mental health care system. There is evidence to indicate that (outside of specialized mental health clinics) appropriate diagnosis and treatment are often not provided in both the general and mental health care systems.

The direct and indirect costs of anxiety disorders to the Canadian economy remain to be investigated. American data, however, provide some information. One study found that persons with anxiety or depressive disorders cost an average of \$2390 (\$US) for a six-month baseline period, compared to \$1397 (\$US) for those without

anxiety or depressive diagnoses. Other studies show that anxiety disorders are also associated with lost or decreased productivity in the workplace.

Treatment of the Anxiety Disorders

Clinicians may treat anxiety disorders from a range of perspectives (e.g., insight-oriented therapy, and hypnosis). However, the treatments with well-recognized empirical support include two main approaches: (1) pharmacotherapy (drug therapy) and (2) cognitive-behavioural therapy (CBT), a form of psychotherapy. Although a few studies have compared these approaches to other treatments (e.g., analytic psychotherapy), these alternative approaches have generally not been especially effective compared to CBT and medication.

Despite a large literature supporting the use of medications and CBT, there remains debate among clinicians and researchers regarding the relative efficacy of both approaches, as well as the relative importance of biological and psychological processes in the etiology of anxiety disorders.

Summary of Main Research Findings

Across each of the anxiety disorders, effective pharmacological (excluding for phobias) and cognitive-behavioural approaches have been developed and empirically validated. There is little consistent evidence that combining CBT and medication is any more effective than using either treatment alone. Panic disorder with (PDA) and without (PD) agoraphobia have been the most extensively researched disorders, whereas specific phobias and posttraumatic stress disorder (PTSD) have been associated with the fewest outcome studies meeting criteria for this review. Few properly controlled studies have been conducted to evaluate the effectiveness of most pharmacological and psychological treatments for PTSD and appropriately diagnosed specific phobias, although preliminary research findings are promising.

The authors identify a number of research findings by type of treatment approach. With reference to *pharmacological treatments*, the authors found that with the exception of specific phobias, certain medications (e.g., alprazolam and clomipramine) have been shown to be helpful for individuals with anxiety disorders.

Preliminary research has shown that selective serotonin reuptake inhibitor (SSRI) antidepressants are useful for most types of anxiety problems. Controlled research studies report that the SSRIs tend to be the pharmacological treatment of choice in studies of OCD. Tricyclic antidepressants appear to be most useful for people with PD and PDA. Monoamine oxidase inhibitor (MAOI) antidepressants (and reversible MAOIs) have been shown to be helpful for several disorders, and they may be the pharmacological treatment of choice for social phobia, at least until additional outcome studies are conducted with other medications. Benzodiazepines appear to be useful for individuals with PD, PDA, social phobia, and GAD. While they bring about the desired effect more quickly than do other interventions, there are withdrawal and rebound effects associated with the discontinuation of the benzodiazepines. Other anxiolytics, such as buspirone, have been shown to be helpful for treating GAD, but not for the other anxiety disorders.

With reference to *psychotherapeutic approaches*, the authors found that cognitive and behavioural treatments are effective methods for decreasing symptoms in each of the anxiety disorders, although few properly controlled studies have been conducted to evaluate the effectiveness of CBT with PTSD and appropriately diagnosed specific phobias. Cognitive-behavioural therapy (CBT) has been shown to be more effective for anxiety disorders than other psychological treatments and is at least as effective as pharmacological approaches. For a variety of disorders, CBT appears to have more lasting effects following termination of treatment than do medications. Among behavioural treatments, exposure-based treatments are effective for phobic disorders as well as for PTSD and OCD. Cognitive interventions are often included in the treatment of PD, PDA, social phobia, PTSD and GAD. They are less often included in the treatment of specific phobias and OCD.

Finally, the authors discuss the findings with respect to *other (non-drug) interventions*, including self-help (self-instruction) treatments (e.g., self-help books) and treatments involving minimal therapist contact (e.g.,

treatment by telephone). With the exception of PD and PDA, little is known about the usefulness of these approaches. However, preliminary studies with specific phobias suggest that these types of treatments may be less effective, compared to studies with PD and PDA.

Potential Directions for Future Research

Based on the findings from the literature review, the authors identify a number of issues which warrant future research. These include risk factors for developing anxiety disorders (in particular for disorders other than PD and PDA) and the role of protective factors in reducing the risk of anxiety disorders among those considered to be vulnerable to developing them.

With respect to *treatment* issues, the authors recommend research on the following issues: the relative and combined efficacy of pharmacological and psychological treatments for PTSD, specific phobias, social phobia and GAD; sequencing of treatments (in cases of combined treatment approaches); and long-term follow-up treatment studies to explore possible differences in treatment efficacy over time. In addition, the authors highlight the importance of further controlled research to evaluate the effectiveness of newer SSRI's and other antidepressant medications in the treatment of the anxiety disorders. Meta-analytic treatment studies, other than for PDA and OCD (where they have been conducted), are recommended. Also recommended is methodologically-sound research on the effectiveness of other forms of psychotherapeutic approaches (e.g., psychodynamic and humanistic approaches) in the treatment of anxiety disorders.

Other research issues identified include: exploring a broader range of treatment outcome variables such as impact on quality of life, future health care utilization costs, lost wages, reduced productivity at work, and impact of treatment on families (including children); and identifying predictors of treatment response (as well as mechanisms by which treatments work) for different groups of patients and for particular individuals, including those with one or more co-morbid conditions.

A number of other issues are highlighted for potential investigation. These include: exploration of the effectiveness of treatment by non-mental health professionals (e.g., family doctors), including the extent to which general practitioners can be trained to administer medications and CBT for anxiety disorders; and examination of the effectiveness of treatments involving minimal therapist contact, especially for disorders other than PD and PDA, and of self-help/mutual aid approaches (e.g., self-help groups). With respect to the latter, preliminary research and anecdotal evidence suggest that many individuals find participation in self-help groups beneficial. Finally, although a critical review of measurement tools for the anxiety disorders was beyond the scope of this review, the authors indicate that evaluation of these instruments is an important area for future research. A compendium and critical review of these instruments could be a useful first step to addressing this issue.

Some research recommendations specific to each type of anxiety disorder were identified. For *PD* and *PDA*, research is needed on the effects of various forms of treatment in specific populations, including the elderly, children, culturally diverse groups, and individuals with multiple psychological problems (e.g., anxiety disorders and substance abuse). For *OCD*, research on psychosocial interventions (e.g., exposure, response prevention, and cognitive therapy) is needed, and more needs to be learned regarding the process of therapeutic change. Many of the older uncontrolled studies should be repeated, using appropriate controls, adequate sample sizes, diagnoses using DSM-IV criteria (as measured by structured interviews), and adequate long-term follow-up. With respect to *social phobia*, further research is needed to confirm preliminary research findings that CBT is at least as effective as pharmacological approaches in the short-term and probably more effective than medications in the long-term. In addition, research on the role of self-help/mutual aid remains to be undertaken. For *GAD*, given that relatively few studies are based on recent criteria, it is important that psychological and pharmacological treatments be evaluated using properly diagnosed patients and a broad range of measures (including cognitive assessments). With respect to *specific phobia*, studies that explore the efficacy of behaviour therapy with a broader range of diagnosed phobias (e.g., heights, storms, flying, et cetera) are needed. In addition, the efficacy of using strategies (e.g., medications,

interoceptive exposure) shown to be effective for treating panic disorder for different specific phobia types remains to be investigated.

Implications for education and other related activities, designed to contribute to improved treatment of the anxiety disorders, are outlined in the

accompanying discussion paper, “Anxiety Disorders: Future Directions for Research and Treatment”.

Chapter 1

INTRODUCTION

Anxiety disorders are among the most common mental health problems. According to the Mental Health Supplement of the 1990 Ontario Health Survey, 9% of men and 16% of women experienced anxiety in the twelve months preceding the survey (Ontario Ministry of Health, 1994). A study of psychiatric disorders in Edmonton, Canada reported lifetime prevalence rates for any anxiety/somatoform disorder of 8.7% for men and 13.8% for women. The overall lifetime prevalence rate (for both sexes) was 11.2% (Bland, Orn, and Newman, 1988). These disorders are often associated with other psychiatric problems, including depression and substance abuse. Anxiety disorders carry substantial personal and societal costs in terms of reduced quality of life, lost wages, decreased productivity, and frequent utilization of health care services (Siegel, Jones, and Wilson, 1990; Swinson, Cox, and Woszczyzna, 1992).

Effective pharmacological, psychotherapeutic, and behavioural interventions exist to treat the anxiety disorders. Recent empirical evidence, however, suggests a lack of knowledge among health and mental health professionals of appropriate treatments for these disorders, and use of treatments that are often not based on empirical, evidence-based research (Swinson et al., 1992).

To contribute to the empirical base of knowledge concerning effective treatment strategies for anxiety disorders, and to further discussions on these issues among stakeholders, a critical review of the treatment literature was commissioned by the Health Promotion and Programs Branch of Health Canada. The report was prepared by Martin Antony, Ph.D, and Richard Swinson, M.D., of the Clarke Institute of Psychiatry in Toronto, Ontario. A companion discussion paper entitled “Anxiety Disorders: Future Directions for Research and Treatment” was also prepared which summarizes the findings of the

critical review, and offers potential directions for future research, educational and care-related activities.

The review includes studies on the six main anxiety disorders: panic disorder with (PDA) and without agoraphobia (PD); obsessive-compulsive disorder (OCD); social phobia; generalized anxiety disorder (GAD); specific disorder; and posttraumatic stress disorder (PTSD). Acute stress disorder, a variant of PTSD with a briefer duration, is not discussed as it was only introduced in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) (American Psychiatric Association, 1994) and there is not yet any published research on treating this disorder. Presumably, the results of studies on PTSD will be relevant to acute stress disorder as well. In addition, agoraphobia without a history of panic disorder, and anxiety disorders induced by a general medical condition or a substance are not discussed, due to the lack of research on specific strategies for dealing with these conditions. Finally, anxiety disorders classified as “not otherwise specified” are not discussed in this review, due to the heterogeneity of this category and the lack of studies describing individuals who receive this diagnosis.

Target Audience

The report should be of interest to health and mental health researchers and to anyone interested in the treatment of the anxiety disorders.

Methodology

Computer literature searches were conducted for papers published in the past 15 years using the Medline and PsychLit data bases. The key words used were combinations of each disorder name and the word “treatment” (e.g., treatment and panic disorder, treatment and obsessive-compulsive disorder). In addition, a manual literature search was conducted by scanning the reference

sections of recent review papers and treatment studies. When available, meta-analytic treatment studies were also reviewed.

Studies were selected for review according to the following criteria:

- ◉ Only controlled research studies were selected for review. These included studies in which specific treatments were compared to alternative treatments, placebos, or no-treatment (i.e., wait-list) comparison groups. The majority of studies reviewed were conducted using a “between-groups” design, although several used a “cross-over” design, in which participants were their own controls.
- ◉ All studies reviewed were required to have at least ten participants per group. It was judged that with fewer than ten participants per group, statistical analyses would be inappropriate and difficult to interpret.
- ◉ All studies reviewed were required to be based on diagnostic criteria from no earlier than DSM-III (American Psychiatric Association, 1980). With the publication of DSM-III, the various anxiety disorders had clear diagnostic criteria that could be replicated across research and clinical sites.
- ◉ Studies of mixed groups of patients (e.g., with panic disorder and generalized anxiety disorder) were not included unless it was possible to separate out the effects of treatment on each disorder. Studies that used structured diagnostic interviews to identify patients with anxiety disorders are identified in the review.

On the basis of these criteria, pharmacotherapeutic studies and studies employing cognitive and behavioural approaches were included for review. Studies of self-help (self-instruction) treatments (e.g., self-help books) and treatments involving minimal therapist contact (e.g., treatment by telephone) were also included where available. However, studies of the effectiveness of (participation in) self-help groups did not meet the criteria and were not included. Studies of other forms of psychotherapeutic interventions (e.g.,

psychodynamic and humanistic approaches) were not included as they did not meet the above criteria. These criteria have both advantages and disadvantages. Although they increased the probability that the studies reviewed would meet certain minimal standards, the criteria may have led to the exclusion of studies, for example, whose findings could have shed light on possible future research directions. In total, over 200 treatment studies were excluded from this review.

Strengths and Limitations of Studies Reviewed

The studies cited in this report represent the existing “state of the art” research of treatment of the anxiety disorders. Nonetheless, these studies may suffer from methodological limitations due to inadequate treatment of the following issues:

- ◉ *Adequacy of treatment delivery:* Dosages and durations (for medication studies) and length of treatment (for psychological treatments) are reported throughout this review. However, it was not always clear whether investigators delivered treatments as reported. For example, with respect to psychotherapeutic studies, it is possible that cognitive behaviour therapists had different levels of skill. It is also possible that participants in the studies were not compliant with the treatment instructions. Furthermore, some of the studies were not consistent in their measurement of treatment compliance and treatment integrity.
- ◉ *Type of outcome measures used:* One limitation of nearly all studies reviewed was their tendency to focus on symptom measurement only, at the expense of measuring functional impairment, quality of life, and other dimensions related to the impact of the disorder on the individual.
- ◉ *Consistency between studies in the types of outcome measures used:* For some disorders (e.g., OCD) the measures tended to be more sophisticated for medication studies than for CBT studies, whereas for other disorders (e.g., GAD), CBT researchers tended to use a broader range of measures than did pharmacotherapy researchers. In general, PD and PDA research is associated with more sophisticated outcome measures than some other disorders (e.g., GAD).

- ◉ *Consistency between studies in the types of assessment (measurement) instruments used:* Assessment instruments are used in both clinical and research settings to determine the presence or absence of symptoms of the anxiety disorders. Many different instruments exist for each of the anxiety disorders, and agreement as to which are the “gold standards” for each specific disorder remains elusive. In addition, many of the instruments tap different domains; for example, some may measure psychological domains, whereas others may measure biological domains. As a result, comparisons between studies, even those that focus on the same anxiety disorder (e.g., social phobia) are often difficult.

Organization of the Report

Chapter 2 provides an overview of the anxiety disorders, and includes information on prevalence, risk factors, patterns of comorbidity, economic costs associated with the disorders, as well as health care utilization by persons with anxiety disorders.

Chapters 3 to 9 provide a critical review of the treatment outcome literature [including pharmacotherapy, psychotherapy (cognitive-

behavioural therapy), and other behavioural interventions, including use of self-help books and treatment by telephone] for each of the six anxiety disorders listed above. Chapter 10 provides a summary and conclusion of key findings, identifies gaps in the research literature, and suggests potential directions for future research.

(Implications for education and related activities are discussed in the accompanying discussion paper).

Appendix 1 provides a table of prevalence rates for the anxiety disorders, and Appendix 2 provides diagnostic criteria for the anxiety disorders drawn from the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994).

Appendix 3 presents a list of useful references on anxiety assessment tools.

Appendix 4 provides brand names and drug classes for each medication cited for each type of anxiety disorder, in addition to a glossary of technical terms and abbreviations used throughout the report.

Chapter 2

OVERVIEW OF THE ANXIETY DISORDERS

Definitions of Anxiety and Fear

Almost everyone would recognize the feelings of anxiety, worry, fear, panic and other similar states. Although many individuals (including clinicians, researchers, and the general public) use these terms interchangeably (e.g., Clark, 1986; Rapee, 1996a), others believe that these terms have distinct meanings (e.g., Antony and Barlow, 1996; Barlow, 1988). In the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), anxiety is defined as an *apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension*. This definition implies that anxiety is a future-oriented state, functioning to motivate the organism to behave in such a way that future danger is averted. Worry is often considered to be a cognitive manifestation of anxiety.

In contrast, fear is viewed by many emotion theorists (e.g., Izard, 1977, 1992; Lang, 1985, 1988) and clinical researchers (e.g., Antony and Barlow, 1996; Beck and Emery with Greenberg, 1985) to be a basic emotion, distinct from anxiety. Fear is associated with a sudden “fight or flight” response to immediate danger, in which the body is prepared for immediate escape from the situation. Fear is assumed to be the same experience that occurs when an individual experiences a panic attack (Craske, 1991). In DSM-IV, a panic attack is a discrete period of intense fear in which at least four symptoms (from a list of 13) begin abruptly and peak over a relatively short period (see Appendix 2). Panic attacks are common across the anxiety disorders and are not a separate codable mental disorder. A number of studies have found that panic attacks are common in the general population (Norton, Cox, and Malan, 1992).

To summarize, anxiety might be the feeling experienced by a nervous driver the day before leaving for a long trip in the car. In contrast, fear might be the emotion experienced when the same driver encounters severe snow and ice on his or her trip. Anxiety is apprehension over some potential future danger, whereas fear and panic tend to be focused on some immediate threat.

The Anxiety Disorders

This section provides a brief summary of the diagnostic criteria for each of the six main anxiety disorders. Complete diagnostic criteria (drawn from the DSM-IV) for panic attacks, agoraphobia, and each of the six main anxiety disorders are provided in Appendix 2.

Panic Disorder with (PDA) and without (PD) Agoraphobia

The hallmark of panic disorder is the experience of recurrent unexpected panic attacks (i.e., panic attacks occurring out of the blue, without any obvious situational trigger), as well as concern about having additional attacks, worry about the consequences of the attacks, or a significant change in behaviour as a result of the attacks. Typically, individuals with PD and PDA report heightened anxiety over experiencing the symptoms associated with panic attacks, such as palpitations, dizziness, and breathlessness (Chambless and Gracely, 1989; Taylor, Koch, and McNally, 1992). PD is often associated with attempts to protect oneself from these sensations by avoiding exercise, sex, and other arousing activities, seeking reassurance (e.g., visiting physicians, checking blood pressure), and avoiding situations in which panic attacks are more likely to occur, or in which escape might be difficult or embarrassing if one were to panic. This type of avoidance is called agoraphobia, and is typically associated with avoidance of such situations as driving, using public transportation, travelling, being alone, being in crowds, and shopping.

Obsessive-Compulsive Disorder (OCD)

OCD is defined by the presence of obsessions (i.e., recurrent and intrusive thoughts, images, or urges that cause marked anxiety) and/or compulsions (i.e., repetitive behaviours or mental acts that are performed to reduce the anxiety generated by one's obsessions). Typical obsessions include concern about contamination, doubting, and disturbing sexual or religious thoughts. Typical compulsions include washing, checking, ordering things, and counting. Individuals with OCD attempt to ignore or suppress their obsessive thoughts, which are not simply excessive worries about everyday problems. In addition, the obsessions or compulsions must be time consuming or distressing to warrant a diagnosis of OCD.

Social Phobia

Social phobia is an excessive or unrealistic fear of social or performance situations. Typical situations feared or avoided by individuals with social phobia include parties, meetings, eating in front of others, writing in front of others, public speaking, conversations, meeting new people, and other related situations. In social phobia, the anxiety is not exclusively related to having the symptoms of another medical or psychiatric condition noticed by others. For example, an individual with Parkinson's disease might feel anxious about having others notice a tremor. Similarly, an individual with an eating disorder might avoid eating in front of others for fear of having unusual eating behaviours noticed. However, these would not be diagnosed as social phobia. To meet full criteria for social phobia, the fear must lead to significant functional impairment or distress. In other words, an individual who fears public speaking, but has no need or desire to speak in front of groups would probably not receive a diagnosis of social phobia.

Generalized Anxiety Disorder (GAD)

The main feature of generalized anxiety disorder is excessive worry occurring more days than not about a number of different domains or activities (e.g., work, finances, family, and health). The worry must be experienced as difficult to control and be associated with at least three of six symptoms, which include restlessness, fatigue, impaired concentration, irritability, muscle tension, and impaired sleep. To meet criteria for GAD, the worry must not be exclusively focused on the features of another disorder (e.g., worrying about having a panic attack, if the individual has PD) and must not occur exclusively during the course of a mood disorder, psychotic disorder, or pervasive developmental disorder. Finally, the worry must lead to significant distress or functional impairment.

Specific Phobia

A specific phobia is an excessive or unreasonable fear of an object or situation (e.g., flying, heights, animals, injections, and blood), usually associated with avoidance of the feared object. The most common objects feared are spiders, bugs, mice, snakes, and heights (Bourdon et al., 1988). The fear must not be related to another disorder (e.g., an individual with agoraphobia who avoids flying due to the possibility of having a panic attack). In addition, the fear must be associated with significant distress or functional impairment.

Posttraumatic Stress Disorder (PTSD)

Posttraumatic stress disorder is a disorder in which an individual experiences a traumatic event involving actual or threatened death or serious injury to oneself or others and responds to the event with intense fear, helplessness, or horror. The fear is associated with three types of symptoms: (1) re-experiencing the event (e.g., nightmares, flashbacks, intrusive memories); (2) avoidance and emotional numbing (e.g., avoiding talking or thinking about the trauma); and (3) symptoms of increased arousal (e.g., sleeplessness, hypervigilance). Symptoms must be present for at least one month and must cause significant distress or functional impairment to be diagnosed as PTSD.

Prevalence and Epidemiology

Prevalence

A number of studies have examined the prevalence of the anxiety disorders. The largest of these studies, conducted in the United States, were the Epidemiological Catchment Area Study (ECA; Bourdon et al., 1988; Eaton, Dryman, and Weissman, 1991; Robins et al., 1984), which included over 18,000 participants, and the National Comorbidity Survey (NCS; Kessler et al., 1994, 1996), which included over 8,000 participants. In addition, a large Canadian community survey of individuals from Edmonton was published based on data from over 3,000 participants (Bland, Orn, and Newman, 1988).

Lifetime prevalence rates for any anxiety disorder, as well as for specific types of these disorders, were reported in each of these studies (see Appendix 1 for a summary of these data). Based on data from three of the five catchment sites, the ECA study reported lifetime prevalence rates for any anxiety disorder ranging from 10.4% to 25.1%. The NCS study reported a 24.9% lifetime prevalence rate for any anxiety disorder. A lower 11.2% rate was reported in the Edmonton study. Possible reasons for these discrepancies in rates are discussed in Appendix 1.

Sex Ratio

Most of the anxiety disorders are more common among women than men. The Mental Health Supplement of the 1990 Ontario Health Survey (Ontario Ministry of Health, 1994) surveyed almost 10,000 Ontario residents using a structured interview based on DSM-III-R criteria (American Psychiatric Association, 1987). The Supplement reported a one-year prevalence rate for anxiety disorders of 9% for men and 16% for women. The data from this preliminary report were not broken down by type of anxiety disorder.

In a review of the literature, Clum and Knowles (1991) found that 59% of patients with panic disorder without agoraphobia (PD) and 89% of patients with panic disorder with agoraphobia (PDA) were female. Kessler et al. (1994) found that 71% of individuals with PD with or without agoraphobia

were women. In contrast, sex differences appear to be smaller in obsessive-compulsive disorder (OCD), with 60% of individuals with OCD being female (Robins et al., 1984). Generalized anxiety disorder (GAD) (Kessler et al., 1994) and posttraumatic stress disorder (PTSD) (Kessler, Sonnega, Bromet, Hughes, and Nelson, 1995) are each about twice as common among women than men, whereas social phobia is more equally distributed across the sexes (Bourdon et al., 1988). For specific phobias, sex ratios vary across specific phobia types. About 70-80% of individuals with phobias of animals, storms, and water are female, whereas the sex ratio is more evenly split for individuals who are phobic of heights (58% female)(Bourdon et al., 1988).

Age of Onset

Several studies have examined the age of onset for various anxiety disorders. Approximate mean ages of onset for the various anxiety disorders are the mid-20s for panic disorder (Burke, Burke, Regier, and Rae, 1990), early 20s for OCD (Rasmussen and Eisen, 1991), mid- to late-teens for social phobia (Mannuzza, Fyer, Liebowitz, and Klein, 1990), and early 20s for GAD (Noyes et al., 1992). For specific phobias, age of onset appears to vary according to phobia type, with phobias of animals, blood, storms, and water beginning in early childhood, phobias of heights beginning in the teens, and situational phobias (e.g., claustrophobia) beginning in the early to mid-20s (for a review, see Antony and Barlow, in press). Although many of the anxiety disorders tend to have an average onset in the 20s, there is variation across the anxiety disorders with respect to the range of ages at which the disorders begin. For example, although specific phobias, GAD, and social phobia often begin in childhood, it is unusual for PD to begin before adolescence.

Patterns of Comorbidity

Most individuals with anxiety disorders do not present with a single disorder. In fact, Sanderson, Di Nardo, Rapee, and Barlow (1990) examined syndrome comorbidity patterns among individuals with anxiety and mood disorders, and found that 70% of individuals (N=130) with a principal anxiety disorder diagnosis met criteria for an additional Axis I disorder, which was often another anxiety disorder. Specific and social phobias were the most common additional diagnoses, affecting about a third of the sample. In addition, a third of individuals with principal anxiety disorder diagnoses met criteria for an

additional depressive mood disorder (i.e., major depression or dysthymic disorder). The frequency of additional diagnoses differed across the anxiety disorders. Percentages of individuals who met criteria for one or more additional disorder(s) were 83% for OCD, 81% for GAD, 69% for PD/PDA, 58% for social phobia, and 53% for specific phobias.

Moras, Di Nardo, Brown, and Barlow (1994) replicated this study using a larger sample (N = 409). In this study, the percentages of individuals meeting criteria for at least one additional diagnosis were 82% for GAD, 56% for OCD, 52% for PDA, 48% for PD, 45% for social phobia, and 20% for specific phobia. In this study, most anxiety disorders had low comorbidity with mood disorders, except for PD with severe agoraphobia (55%) and OCD (40%). The most frequently diagnosed additional diagnoses were GAD (23%) and social phobia (14%).

Several smaller studies have examined the prevalence of comorbid conditions in patients with anxiety disorders. van Ameringen, Mancini, Styan, and Donison (1991) found in a study of 57 patients with social phobia that 70% of these individuals suffered from at least one additional disorder in their lifetimes. Lifetime prevalences of additional disorders in individuals with social phobia were 49.1% for PD/PDA, 28.1% for alcohol abuse, and 15.8% for substance abuse or dependence. Where comorbidity was present, social phobia predated mood disorders in 81.7% of cases and predated other anxiety disorders in 62.7% of cases.

There is evidence that bipolar disorder may be associated with PD. Using the 1984 Epidemiological Catchment Area Survey database, Chen and Dilsaver (1995) examined the prevalence of comorbid panic disorder among individuals with histories of unipolar depression (N=792), bipolar disorder (N=168), and among individuals without histories of either disorder (N=17,143). These authors found that

the prevalence of PD among those individuals with neither unipolar or bipolar disorder was .8%, whereas the prevalence of PD among individuals with unipolar depression and bipolar disorder was 10% and 20.8%, respectively.

A variety of studies have examined the prevalence of other disorders in patients with anxiety disorders. Several studies have shown that alcohol and substance abuse are associated with anxiety disorders, particularly for individuals with social phobia and PDA (Cox, Norton, Swinson, and Endler, 1990; Kushner, Sher, and Beitman, 1990). In addition, Sanderson, Beck, and Betz (1991) interviewed 355 individuals with anxiety disorders and found that 35% had at least one comorbid personality disorder. Personality disorders were especially common among patients with social phobia (61%) and GAD (49%) and least common among those with specific phobias (12%). This finding that anxiety disorders are often associated with personality disorders has been confirmed in a variety of other studies (Stein, Hollander, and Skodol, 1993).

A number of studies have examined the impact of treatment for one disorder on comorbid conditions. Fava, Zielezny, Luria, Canestrari (1988) found that behavioural treatment of agoraphobia led to changes in comorbid obsessive-compulsive symptoms. Similarly, Brown, Antony, and Barlow (1995) found that patients with PD who underwent CBT experienced a decrease in comorbid conditions as well. Comorbidity was not predictive of treatment outcome.

Risk Factors¹

According to the Mental Health Supplement of the Ontario Health Survey (Ontario Ministry of Health, 1994), risk factors for developing an anxiety disorder include surviving severe abuse, and parental mental disorder. These were also risk factors for all disorder types listed in the report, including mood disorders, substance abuse, depression, and antisocial behaviour. The Supplement did not examine risk factors for particular anxiety disorders. A number of related socio-

1 Although this review does not focus on anxiety disorders induced by a general medical condition or substance, it is recognized that individuals may experience anxiety due to, for example, the presence of a physical illness (e.g. hyperthyroidism) or drug use (either illicit, prescription, or over-the-counter medications).

demographic variables were also reported. Similar rates of unemployment for those with anxiety disorders (7%) and for those without these disorders (6%) were noted. However, 8% of persons with anxiety disorders received public assistance, compared to 3% of the “healthy” group. Similarly, 15% of those with anxiety disorders were in low-income households compared to 9% of those without these disorders. Siegel et al., (1990) report that among men, those with panic disorder, obsessive-compulsive disorder, or phobias were more likely to be chronically unemployed and to be receiving financial assistance or welfare.

Family history of anxiety has been identified as a risk factor for developing anxiety disorders. A number of studies have shown that each of the anxiety disorders tends to run in families, and there is evidence that the relationship among anxiety disorders in different family members may be genetically mediated to some extent (Fyer, Mannuzza, Chapman, Martin, and Klein, 1995; Kendler, Neale, Kessler, Heath, and Eaves, 1992; MacDonald and Murray, 1994; Pauls, Alsobrook, Goodman, Rasmussen, and Leckman, 1995).

Several risk factors have been identified for individual anxiety disorders. Risk factors for developing PD and PDA include the occurrence of stressful life events such as loss, illness, and marital conflict (Faravelli and Pallanti, 1989), the perceived negative impact of stressful events (Roy-Byrne, Geraci, and Uhde, 1986), and even the anticipation of a major life event (Pollard, Pollard, and Corn, 1989). Being female is also a risk factor for PD, as well as for specific phobia and GAD. Anxiety in childhood appears to be a predictor of developing PDA or GAD in adulthood (Angst and Vollrath, 1991; Aronson and Logue, 1987). In addition, alcohol withdrawal (Kushner, Sher, and Beitman, 1990), cannabis use (Roy-Byrne and Uhde, 1988), and cocaine use (Aronson and Craig, 1986) may trigger panic attacks in some individuals. PD is more common in people under 65 years of age than in those over 65 years (Keyl and Eaton, 1990).

Parental behaviour (e.g., a tendency to be overprotective, less affectionate, and more controlling) appears to be associated with the development of PD and other anxiety disorders in adulthood (Gerlsma, Emmelkamp, and Arrindell, 1990; Silove, Parker, Hadzi-Pavlovic, Manicavasagar, and Blazczynski, 1991). Individuals with social phobia describe their parents as having discouraged them from socializing, placed undue importance on the opinions of others, and used shame as a means of discipline compared to non-anxious controls (Bruch and Heimberg, 1994). Other predictors of developing social phobia include a childhood history of separation anxiety, shyness in childhood, and infrequent dating (Bruch, 1989; Bruch and Heimberg, 1994).

Experiencing a traumatic event puts people at risk for developing PTSD (according to the definition of PTSD) as well as for certain phobic disorders. A substantial proportion of individuals with specific and social phobias report an onset associated with a traumatic event (Antony and Barlow, in press). In fact, in some studies (e.g., Öst, 1985) this proportion is greater than 50%. However, it should be noted that many individuals experience traumatic events and do not develop PTSD or a phobic disorder. It has yet to be determined which variables influence whether an individual is likely to develop an anxiety disorder following a traumatic event. Possible variables that may mediate individual variability in response to traumatic events include degree of stress experienced at the time of the event, the context of the event, social support following the event, biological predispositions, and personality features of the individual.

More research is needed regarding risk factors for developing anxiety disorders. This is especially the case for disorders other than PD and PDA. In addition, there are virtually no studies that have examined the role of protective factors that might decrease the tendency to develop anxiety disorders among those considered to be at risk.

Theories of Etiology

Theories of anxiety disorders have come from a broad range of perspectives, ranging from psychodynamic perspectives (e.g., Nemiah, 1981; Shear, Cooper, Klerman, Busch, and Shapiro, 1993) to evolutionary models (e.g., Marks and Nesse, 1994; Nesse, 1987). However, the most influential theoretical models for the anxiety disorders have come from two broad perspectives: cognitive-behavioural and biological. Debate exists among researchers and clinicians as to the relative importance of each of these perspectives in explaining the etiology of anxiety disorders. Differences in perspectives also impact on choice of treatment approach (i.e., pharmacotherapy versus psychotherapy).

As reviewed by Antony, Brown, and Barlow (1992), biological theorists tend to minimize the importance of psychological variables, citing research on differences between individuals with and without anxiety disorders on a variety of biological variables (e.g., brain imaging, hormone levels, biological challenges, neurochemical levels, and genetics). Cognitive and behavioural theorists explain these findings as biological manifestations of a primarily cognitive or behavioural phenomenon and often cite studies demonstrating that these biological findings can be influenced by psychological variables. In addition, cognitive-behavioural theorists point to data showing fear-relevant biases of attention and memory as well as anxious beliefs regarding feared objects and situations among individuals with anxiety disorders. For biological theorists, these findings tend to be explained as cognitive manifestations of a primarily biological process.

According to Antony et al. (1992), biological and psychological findings can generally be explained from either perspective and there is little reason to accept only one of these views. A more parsimonious approach is one that integrates biological and psychological findings. Recent models of anxiety disorders (e.g., Antony and Barlow, 1996; Barlow, 1988) have attempted to account for the ways in which both biological and psychological factors influence the development of anxiety disorders.

Cognitive and Behavioural Theories

Although cognitive and behavioural models of anxiety are often grouped together, the proponents of each perspective tend to emphasize different variables in their theories. Behavioural theorists tend to focus on learning experiences involving classical and operant conditioning that lead to the development and maintenance of fear. An example of a behavioural model is Mowrer's (1960) two-stage model of fear development and maintenance. According to Mowrer, fear begins with a classical conditioning event, in which an object is paired with some aversive event so that the organism learns to fear the object. Fear is maintained by operant conditioning, in which avoidance behaviour leads to a decrease in fear, which in turn reinforces the avoidance.

Rachman (1976, 1977) challenged this view on the grounds that many individuals with phobias do not recall a specific conditioning event that led to their phobia. He proposed that although conditioning may be one cause, phobias may also begin by vicarious conditioning (e.g., observing another individual behave fearfully) or by informational onsets (e.g., being told that a particular situation is dangerous). Rachman's model is an example of a theory that integrates learning and cognitive processes. Cognitive theorists emphasize the importance of beliefs, predictions, interpretations, and cognitive biases in the development and maintenance of disorders.

Perhaps the best known cognitive model of anxiety disorders is David Clark's (1986, 1988) model of PD. According to Clark, unexpected panic attacks are triggered by the occurrence of normal physical sensations that are catastrophically misinterpreted by the individual as indicative of some immediate threat. This misinterpretation leads to heightened anxiety, which in turn leads to more sensations and more catastrophic interpretations. Very quickly, what began as mild physical arousal spirals into a panic attack.

Numerous variations on these cognitive and behavioural models have been proposed to explain each of the anxiety disorders. Several recent books contain excellent reviews of cognitive and behavioural models for anxiety disorders (e.g., Heimberg, Liebowitz, Hope, and Schneier, 1995; McNally, 1994; Rapee, 1996b; Rapee and Barlow, 1991).

Biological Models

For the most part, biological models of anxiety disorders have focused on particular neurotransmitter systems. In the case of PD, the noradrenergic system has been most thoroughly researched (Charney et al., 1990), although, recently, there has been some interest in the cholecystokinin (CCK) system as well (Bradwejn, 1995). For OCD, the serotonergic system seems to be the most important system (Liebowitz and Hollander, 1991). Researchers interested in GAD have focused primarily on the GABA-benzodiazepine system (Cowley and Roy-Byrne, 1991). With respect to social phobia, some researchers have suggested that the dopamine may be most relevant (Levin, Schneier, and Liebowitz, 1989). Of course, it is likely that a variety of neurotransmitters acting across different areas of the brain are involved in the etiology and maintenance of anxiety and fear.

Recent models (e.g., Antony and Barlow, 1996; Barlow, 1988) have integrated psychological and biological approaches. Interestingly, in the case of generalized anxiety disorder (GAD), research has indicated that alprazolam (a benzodiazepine) seems to lead to a reduction of the somatic symptoms of GAD, whereas imipramine (a tricyclic antidepressant) leads to greater improvement in psychic symptoms (e.g., negative thinking and dysphoria). More research is needed before the biological foundations of anxiety can be understood.

Health Care Utilization and Economic Costs

Recently, several investigators have begun to examine patterns of health care utilization and the economic consequences of having an anxiety disorder.

Health Care Utilization

In a U.S. study, Siegel, Jones, and Wilson (1990) estimated that compared to the general population, individuals with panic disorder, on an annual basis, use psychiatric and non-psychiatric services seven times more often than the general population. (This figure was extrapolated from the findings of a pilot study that explored use of health care services in the

past month.) In addition, these individuals miss twice as many work days as the general population. Leon, Portera, and Weissman (1995) found that nearly 30% of those in the 1984 Epidemiological Catchment Area study (in the United States) diagnosed with panic disorder had used the general medical system for their emotional well-being. In addition, individuals with an anxiety disorder were more likely than those who were not anxious to seek help in emergency rooms and with specialized mental health care practitioners.

Pollard, Henderson, Frank, and Margolis (1989) also report that persons with anxiety disorders have frequent contact with the general health care system. These authors interviewed 142 individuals from the general population in the United States who met diagnostic criteria for an anxiety disorder according to structured interviews. Forty percent of agoraphobics, 28% of those with OCD, and 8% of those with social phobia had sought professional assistance. Individuals living in the city were more likely to seek help than those living outside the city. Of those who sought help, almost half did not seek help from a mental health professional, but rather were seen by non-psychiatric physicians and members of the clergy.

In a Canadian study (N=128), Swinson, Cox, and Woszczyzna (1992) found that nearly a third of individuals with PDA or social phobia had seen at least three different health care practitioners in the previous year. Among the group with PDA, 21% had gone to a hospital emergency room, 9% had been hospitalized, 9% had been seen by a cardiologist, and 17% had been seen by a neurologist specifically for anxiety-related complaints at some point in their lives. Two-thirds of these individuals had also seen a psychiatrist.

Although there is evidence that individuals with anxiety disorders have frequent contact with the health care system, evidence suggests that they may not receive the most appropriate treatment from both general practitioners and mental health specialists. Swinson et al. (1992) found that although the majority of patients with panic disorder and social phobia had tried psychotropic medications (89% and 75%, respectively), most had never received the treatments with the most empirical support. Among patients with PD, only 15% had received imipramine, 13% had received alprazolam, and 11% had received cognitive-behavioural therapy. Only 4% of patients with social phobia had received monoamine oxidase inhibitors and 4% had received cognitive-behavioural therapy.

These authors suggest that education regarding early recognition and intervention is needed for general and emergency department physicians. Education of other health professionals, such as occupational therapists, social workers, and psychiatric nurses, would also be important. Swinson et al. suggest that seminars on the different types of anxiety disorders and corresponding treatments, and standardized methods of assessment would help to address the issue of (use of) inappropriate treatments.

Other studies have reported similar findings. A survey of psychiatrists and psychiatric residents (McCarley, Steinberg, Spears, and Essock-Vitale, 1987) showed that psychiatric professionals are more likely to favour biological approaches over behavioural approaches in their training and practice. In addition, psychoanalytic and psychodynamic approaches were favoured over CBT despite the lack of empirical support for these treatments. A recent survey of family practice physicians (Hecker, Fink, and Fritzler, 1993) was somewhat more optimistic in its findings. Participants tended to rate CBT as a more acceptable treatment for PD than client-centered therapy, with pharmacological approaches falling somewhere between the two psychological approaches in terms of acceptability.

Results were more promising in specialized anxiety disorders clinics. Swinson, Cox, Kerr, Kuch, and Fergus (1992) sought to investigate the availability and appropriateness of services for anxiety disorders in Canada. They sent a questionnaire to 240 hospitals across the country, of which 117 responded. Of the responding hospitals, only 18 had an anxiety disorders clinic. Clinics saw an average of 208 patients per year. The most common diagnoses seen were PDA (25.4%), GAD (22.1%), PD (15.2%), social phobia (13.5%), agoraphobia without panic (9.9%), OCD (8.9%), and PTSD (8.8%). Despite the high prevalence of specific phobias in the general population, these individuals tended not to present to anxiety disorders clinics. Most of the clinics reported having an orientation consistent with CBT, pharmacotherapy, or combinations of these approaches.

Economic Costs

Although a thorough examination of the estimated costs of anxiety disorders to the Canadian economy remains to be done, estimates of the costs to the economies of other countries are revealing. Simon, Ormel, VonKorff, and Barlow (1995) investigated health care costs associated with anxiety disorders and depressive disorders among primary care patients in the United States. Patients with a DSM-III-R anxiety or depressive disorder were compared to patients without significant mood or anxiety symptoms. Those with anxiety or depressive disorders cost an average of \$2390 (\$US) for a six-month baseline period, compared to \$1397 (\$US) for those without anxiety or depressive diagnoses. Most of the costs associated with anxiety disorders and depression were related to use of general medical services rather than mental health treatment costs (even after controlling for the presence of comorbid medical illness).

Salvador-Carulla, Segui, Fernandez-Cano, and Canet (1995) estimated the direct health care costs (e.g., therapeutic visits, hospitalization, treatment, medications, alternative medicine) and indirect costs (i.e., lost work productivity) of panic disorder before and after psychiatric diagnosis and treatment for 61 outpatients at a psychiatric clinic in Spain. From the 12-month period preceding the first visit to the clinic (the pre-diagnostic period) to the 12-month period following the first visit (the post-diagnostic period), the frequency of visits to non-psychiatric physicians decreased from 313 to 15 (mean of 5.13 per person to 0.25 per person). Visits to hospital emergency rooms decreased from 75 to 7 (mean of 1.23 per person to 0.11 per person). Similarly, medical tests administered decreased significantly following diagnosis. However, as a result of psychiatric diagnosis and subsequent treatment (using psychotropic drugs), the number of psychiatric visits increased from 40 to 793. Overall, direct health care costs increased from a mean per patient of \$478 (\$US) before diagnosis to \$758 (\$US) after diagnosis, largely due to psychiatric visits and medication costs. The mean indirect costs of decreased work productivity were \$1076 (\$US) per person in the year preceding diagnosis and \$228 (\$US) in the year following diagnosis. The authors note that their study suffers from possible methodological weaknesses which may have presented potential biases in the findings (see Salvador-Carulla et al., 1994 for a discussion of the methodological limitations).

Chapter 3

REVIEW OF THE TREATMENT OUTCOME LITERATURE

The treatment of anxiety disorders has become a very popular area of research. A survey of 14 journals representing psychology and psychiatry (Cox, Wessel, Norton, Swinson, and Direnfeld, 1995) found that 30% of the 432 anxiety disorders studies published between 1990 and 1992 were treatment studies. The percentages of studies on each type of disorder were 39.1% for PD/PDA, 7.6% for social phobia, 5.1% for specific phobia, 7.2% for GAD, 14.1% for PTSD, and 15.5% for OCD.

A range of treatment approaches exist for the anxiety disorders, such as insight-oriented therapy and hypnosis. However, the treatments with empirically validated support include two main approaches: (1) pharmacotherapy (drug therapy) and (2) cognitive-behavioural therapy (CBT), a form of psychotherapy. Although a few studies have compared these approaches to other treatments (e.g., analytic psychotherapy), these alternative approaches have generally not been especially effective compared to CBT and medication.

Despite a large literature supporting the use of medications and CBT, there is still much debate among clinicians and researchers from different etiological perspectives regarding the relative and combined efficacy of medications and CBT. Investigators from biological and psychological perspectives rarely collaborate on treatment studies and rarely read one another's work, except to criticize it. Biological and psychological treatment studies tend to be conducted at different sites, use different assessment and outcome measures, and get

published in different journals. Over time, more investigators and clinicians have been willing to consider multidimensional approaches to understanding and treating anxiety disorders, but there is still much work to be done to educate practitioners and researchers about the nature of anxiety disorders and their treatment.

The following review of treatment studies discusses the relative and combined effectiveness of pharmacological and cognitive-behavioural approaches in the treatment of anxiety disorders. Studies on self-help (self-instruction) treatments (e.g., self-help books) and treatments involving minimal therapist contact (e.g., treatment by telephone) are also discussed. Effective pharmacological treatments examined include antianxiety medications (i.e., benzodiazepines), antidepressants, and several other types of medication. In addition, a variety of psychological strategies have been shown to be useful for treating anxiety. These include cognitive (e.g., cognitive restructuring, coping self-statements) and behavioural approaches (e.g., in vivo exposure, interoceptive exposure, applied relaxation training, social skills training, applied tension). These approaches are each defined in Appendix 4. Readers are also referred to this Appendix for a listing of brand names and drug classes for each (generic) medication name cited, as well as a glossary of technical terms and abbreviations, used in the following chapters.

Chapter 4

PANIC DISORDER AND AGORAPHOBIA

Introduction

Panic disorder (PD) and panic disorder with agoraphobia (PDA) are the most researched of the anxiety disorders. A variety of approaches have been repeatedly shown to be effective for treating these conditions. Among medications, the most researched drugs are alprazolam and imipramine. In addition, controlled studies have been conducted with a variety of other medications including benzodiazepines (e.g., clonazepam, adinazolam), antidepressants (e.g., clomipramine), and other drugs (e.g., inositol, CCK antagonists). The main psychological approaches studied include cognitive strategies (e.g., cognitive restructuring) and behavioural strategies (e.g., in vivo exposure, interoceptive exposure, breathing retraining, relaxation training).

In addition to the controlled studies reviewed in this section, there are numerous smaller, uncontrolled studies that were not reviewed. Some of these have been replicated by similar studies with more advanced methodological designs. Other studies have examined specific questions that have yet to be addressed in larger, controlled studies. These include studies of new treatments that are still in their early stages of investigation (e.g., treatments that use computers to deliver CBT).

Medication Studies

Alprazolam Studies

The Cross National Collaborative Panic Study (Ballenger et al., 1988) was the largest study ever conducted to evaluate the efficacy of alprazolam, a benzodiazepine-derivative. Patients (N = 526) with DSM-III diagnoses of agoraphobia with panic attacks or panic disorder with agoraphobia (based on structured interviews) were randomly assigned to

eight weeks of alprazolam or placebo. Mean alprazolam dosages were 4.9 mg/day at week 4 and 5.7 mg/day at week 8. Analyses of plasma benzodiazepine levels suggested that the vast majority of patients were compliant with treatment. As early as week one, alprazolam was significantly more effective than placebo on a variety of measures, including panic frequency, phobic fear and avoidance, anxiety, and secondary disability. By week 8, 92% of patients taking alprazolam and 63% of patients taking placebo were considered to be at least moderately improved (physician-rated global improvement scale). The percentage of patients who were panic-free (end-point analysis) by week 8 were 55% and 32% for alprazolam and placebo, respectively. Overall, alprazolam was accepted by patients, and there were few serious side effects (Noyes et al., 1988). Common side effects early in treatment included sedation (61.7%), fatigue (23.4%), ataxia (an inability to coordinate voluntary muscular movements) (28.5%), slurred speech (19.5%), and amnesia (12.1%). Side effects decreased over the course of treatment. Consistent with current diagnostic nomenclature suggesting that agoraphobic avoidance is secondary to panic attacks, panic attacks tended to improve before phobic avoidance (Rifkin et al., 1990).

Several studies have examined predictors of outcome in the Cross National Collaborative Panic Study. Greenblatt, Harmatz, and Shader (1993) examined the relationship between alprazolam plasma levels and treatment efficacy in a subset of patients (N = 237) from the Cross National Study. Early in treatment, plasma levels of alprazolam seemed to be related to efficacy, but this relationship disappeared by the end of week 8. Lesser et al. (1988) found that comorbid secondary major depressive episodes did not affect outcome. Alprazolam was effective at decreasing depressive symptomatology in patients with PD and PDA. Finally, Woodman et al. (1994) examined a variety of variables and found that the strongest predictors of response to alprazolam were age (over age 40) and lower baseline levels of anxiety and phobic avoidance.

Sustained-Release Alprazolam

Two studies have recently evaluated the efficacy of a new sustained-release formula for alprazolam (Pecknold, Luthe, Munjack, and Alexander, 1994; Schweizer, Patterson, Rickels, and Rosenthal, 1993). Participants were diagnosed using structured interviews and treatment lasted six to eight weeks. Overall, sustained release alprazolam was more effective than placebo, although not significantly different than regular formula alprazolam.

Alprazolam Discontinuation Studies

Two reports have been published regarding discontinuation of alprazolam in patients from the Cross National Collaborative Panic Study. The first report (Pecknold, Swinson, Kuch, and Lewis, 1988) described the effects of discontinuation over a period of four weeks for 126 patients who took either alprazolam or placebo for eight weeks. Overall, discontinuation led to significant relapse in the alprazolam-treated group but not the placebo-treated group. However, by the end of the taper, differences were no longer significant, as patients who took alprazolam regained some of their improvement. A withdrawal syndrome was present during discontinuation for 35% of patients in the alprazolam-treated group, but none in the placebo group. Withdrawal symptoms included confusion, disorientation in time, place or person, heightened sensory perception, dysosmia (abnormality in taste or smell), paresthesias (sensation of numbness or tingling), muscle twitch, muscle cramp, blurred vision, diarrhea, decreased appetite and weight loss, and muscle cramps. These were not incapacitating or life-threatening in any of the cases.

The second study (DuPont et al., 1992) examined the effects of discontinuation over four weeks in 142 patients who took alprazolam for an additional five to 12 months following the eight-week active treatment phase in the Cross National Study. There were large site differences in patients' ability to discontinue alprazolam. At two sites, 90% and 95% of patients were able to discontinue their medication, whereas 21%, 38%, and 66% were able to discontinue alprazolam at the other three sites.

Noyes, Garvey, Cook, and Suelzer (1991) studied 50 patients with DSM-III-R diagnoses of PD (by structured interview) who had been taking alprazolam, diazepam, or placebo for eight months. Gradual discontinuation took from one to five weeks. Following discontinuation, the majority of patients in the active treatment groups relapsed (63% to 84% depending on the criteria used), with no differences between the groups. Rebound and withdrawal symptoms were more common following discontinuation from alprazolam than diazepam, but not significantly so on most measures. Like studies of regular alprazolam, discontinuation (in less than five weeks) of sustained-release alprazolam led to increased levels of distress in 48% of patients taking the drug and only 10% of patients taking placebo (Schweizer et al., 1993).

One criticism of studies examining discontinuation is that the tapering of medication often occurs over a very brief period. In a naturalistic study, Abelson and Curtis (1993) examined the effects of gradual discontinuation (mean 7.7 months) in 20 DSM-III-R panic disorder patients (diagnosed by structured interview) who were taking an average of 4.1 mg/day of alprazolam in a 12-week treatment study. Seventy-eight percent of patients were able to discontinue their medication, of which relapse occurred in about a third. At follow-up (11 to 26 months), 61% of patients were medication-free and 28% were taking a benzodiazepine.

Because of the difficulty that most patients with PD have discontinuing treatment with alprazolam and other benzodiazepines, investigators have begun to develop specific programs to help patients stop taking anxiolytics. Klein, Colin, Stolk, and Lenox (1994) examined the efficacy of carbamazepine (compared to placebo) in helping 36 individuals with PD (DSM-III-R diagnoses confirmed by structured interview) discontinue treatment with alprazolam (mean dosage 3.96 mg/day). Carbamazepine was significantly superior to placebo for helping individuals discontinue alprazolam, particularly for those subjects taking low dosages of alprazolam (less than 4 mg/day).

Finally, two recent studies have examined the use of cognitive-behavioural therapy (CBT) in helping individuals with panic disorder to discontinue alprazolam. Otto et al. (1993) randomly assigned patients (N = 33) taking alprazolam or clonazepam for PD for at least six months to one of two taper conditions: (1) slow taper condition; or (2) slow taper plus ten sessions of CBT.

Patients who received CBT were significantly more likely (76%) to be successful at discontinuing their medication than were those who did not receive CBT (25%). At three-month follow-up, 77% of patients in the CBT group remained benzodiazepine-free. Unfortunately, this study did not provide many details regarding diagnostic criteria for subject selection.

In another study (Spiegel, Bruce, Gregg, and Nuzzarello, 1994), 21 patients meeting DSM-III-R criteria for PD or PDA (by structured interview) and who were panic-free following treatment with alprazolam (mean dose = 2.2 mg/day; mean duration = 6.3 weeks) were randomly assigned to discontinue the medication by: (1) supportive drug maintenance and slow flexible taper; or (2) identical procedure with the addition of 12 sessions of CBT. There were no differences in the rate of discontinuation (80% in the alprazolam-only group; 90% in the alprazolam plus CBT group). However, by three month follow-up, only 40% of patients in the alprazolam-only group had maintained their drug-free status, whereas all patients in the alprazolam plus CBT group who were able to discontinue their medication were able to remain drug-free through the entire six-month follow-up period. Interestingly, the best predictor of relapse in this study was the post-taper change in anxiety sensitivity (i.e., anxiety over fear symptoms). Post-taper change predicted drug status at follow-up in 85% of cases (Bruce, Spiegel, Gregg, and Nuzzarello, 1995).

Single-Drug Trials with Other Benzodiazepines

Beauchair, Fontaine, Annable, Holobow, and Chouinard (1994) randomly assigned 32 patients with DSM-III diagnoses of PD or agoraphobia with panic attacks to four weeks of treatment with clonazepam (mean dosage 2.2 mg/day) or placebo. By the end of treatment, clonazepam was superior to placebo at reducing panic frequency, duration, and intensity, as well as symptoms of anxiety and depression. For some measures (e.g., PD severity), there was a significant correlation between plasma concentration of clonazepam and outcome. Drowsiness was the most common side effect, occurring in 69% of participants taking the drug.

Two studies have been conducted using sustained-release adinazolam to treat panic disorder. In a double-blind study of 206 patients with DSM-III-R diagnoses of PDA (confirmed by structured interview) Davidson et al. (1994) compared four weeks of treatment by sustained-release adinazolam (mean dosage at week four = 84.1 mg/day) to placebo. The percentages of participants receiving global impression ratings of “much improved” or “very much improved” were 69.7% and 39.6% for adinazolam and placebo-treated patients, respectively. In addition, adinazolam led to complete blocking of panic attacks in a higher percentage of patients than did placebo (57.1% versus 39.2%). Adinazolam led to greater improvement than placebo on a variety of measures including global improvement, panic frequency, phobic severity, and anticipatory and general anxiety. Differences were not significant for self-rated phobia severity, unexpected or situational panic, or disability measures (e.g., work, family, social).

In the second study (Carter et al., 1995), 315 patients with DSM-III-R diagnoses of PDA (confirmed by structured interviews) were randomly assigned to four weeks of treatment by placebo or one of three dosages of sustained-release adinazolam (30 mg, 60 mg, 90 mg). On most measures (including measures of panic frequency and some measures of phobic avoidance), 60 and 90 mg dosages were more effective than 30 mg and placebo after four weeks of treatment. Patients with a history of recurrent major depression (but not single episodes only) had a poorer response to treatment than patients with no history of major depression (Maddock et al., 1993).

Imipramine Studies

Mavissakalian and Perel (1988; 1995) studied 80 individuals meeting DSM-III criteria for agoraphobia with panic attacks or DSM-III-R criteria for PDA. Patients were randomly assigned to eight weeks of treatment with placebo or one of three dosages of imipramine (.5 mg/kg/day; 1.5 mg/kg/day; or 3 mg/kg/day). Dropout rates for the low, medium, and high dosage groups were 6%, 15%, and 36%, respectively. Overall, the medium and high dosages led to significantly more improvement in panic, phobic symptoms, and general functioning than did the low dosage and placebo groups, which did not differ from one another. Similarly, medium and high dosages did not differ from one another in their effectiveness. Response was correlated with plasma levels of imipramine; however, beyond levels of 140 mg/ml, no

additional benefits were observed for panic, and higher levels were associated with a detrimental effect on phobic symptoms.

In another study, Mavissakalian and Perel (1992a; 1992b) followed 24 weeks of successful acute treatment with imipramine with either: (1) discontinuation of the imipramine following the acute phase (n = 16); or (2) discontinuation following an additional year of maintenance treatment at half the dosage taken during the acute phase (n = 14). In the six months following discontinuation, patients who received maintenance treatment with imipramine were significantly less likely to relapse than were patients who were discontinued immediately after the acute phase.

Single-Drug Trials with Other Medications

Johnston, Troyer, and Whitsett (1988) investigated the efficacy of clomipramine in a double-blind study of 108 patients meeting DSM-III criteria for agoraphobia. Patients were randomly assigned to eight weeks of treatment with clomipramine (mean dosage at week 8 = 82.8 mg/day) or placebo. Clomipramine was superior to placebo on a variety of measures, including measures of depression, panic frequency, and phobic anxiety.

In two studies of clonidine in patients meeting DSM-III criteria for PD (using structured interviews), Uhde et al. (1989) examined the effects of intravenous clonidine for one hour and oral clonidine for a mean of 10 weeks (mean dosage = .4 mg/day). In the first study, 12 patients with PD and 10 normal controls were given clonidine and placebo intravenously in random order on two separate days. Clonidine led to greater changes in state anxiety and physiological correlates of anxiety than did placebo. Changes were more marked for patients with PD than for normal controls. In the second study, patients began a trial of clonidine after being on placebo for at least three weeks. Oral clonidine failed to show any anxiolytic benefit on a variety of measures.

Despite findings that L-365,260 (a CCK_B antagonist) blocks CCK-4 induced panic, Kramer et al. (1995) found that six weeks of treatment with L-

365,260 (30 mg qid) had little effect on measures of global improvement, anxiety, panic or disability, relative to placebo. Participants were 88 patients diagnosed with PD or PDA according to DSM-III-R criteria.

Finally, Benjamin et al. (1995) compared four weeks of treatment with 12 g/day of the intracellular second-messenger precursor inositol (an isomer of glucose and a natural component of the human diet) and a placebo in a crossover study with 21 patients with DSM-III-R diagnoses of PD or PDA. The frequency and severity of panic attacks as well as phobic symptoms decreased more after treatment with inositol than with placebo, with minimal side effects.

Studies Comparing Alprazolam and Imipramine

The largest study to compare imipramine and alprazolam was that conducted by the Cross National Collaborative Panic Study, Second Phase Investigators (1992) across 12 international centres. In this study, 1168 patients with DSM-III diagnoses of PD (diagnosed by structured interviews), were randomly assigned to eight weeks of double-blind treatment with imipramine (mean dosage at week eight = 155 mg), alprazolam (mean dosage = 5.7 mg), or placebo. Outcome measures included global improvement ratings, panic attack diaries, phobia ratings, measures of generalized anxiety and depression, and social functioning.

For most measures, improvement was noted with alprazolam by week one or two and with imipramine by week four. By week eight, patients in the alprazolam and imipramine groups had improved equally and were more improved than those in the placebo group on most measures. Seventy percent of those in the imipramine and alprazolam groups and 50% of those in the placebo group were panic-free at the end of treatment. Side effects were more common early in treatment than at the end of eight weeks for both drugs. At week eight, common side effects for imipramine included dry mouth (43%), constipation (23%), excessive sweating (19%), and increased appetite (14%). Common side effects for patients taking alprazolam included sedation (29%), memory problems (14%), fatigue (13%), and constipation (12%). Final outcomes for patients taking alprazolam were predicted by improvement in the number of spontaneous panic attacks in the first week of treatment, whereas placebo response was predicted by early improvements in

anticipatory anxiety. Improvements among patients taking imipramine could not be predicted in the first week of treatment (Albus et al., 1990).

Katschnig et al. (1995) re-interviewed 367 patients four years after they had participated in the original Cross National Collaborative Panic Studies (Phase I and Phase II). Sixty-one percent of patients still had at least occasional panic attacks, although only 16.7% still had significant phobic avoidance and very few reported serious impairment from their symptoms. Long-term outcome was related to longer duration of illness and more severe pre-treatment phobic avoidance, but not to the specific medication used during the study or to the use of medications during the follow-up period.

Because both Cross National Collaborative Panic Studies excluded patients with major depression, Keller et al. (1993) conducted a study to evaluate alprazolam, imipramine, and placebo in 126 patients with comorbid diagnoses of PDA and a depressive disorder (DSM-III-R criteria according to a structured interview). At the end of treatment (16 weeks) mean dosages of imipramine and alprazolam were 159.3 mg/day and 5.25 mg/day, respectively. By the end of treatment, medications were no more effective than placebo for measures of panic (75% to 79% of patients in each group had no panic attacks during week 16). However, both active treatments did lead to more improvement than placebo on anticipatory anxiety, depression, and general functioning. Overall, there were no differences between alprazolam and imipramine by week eight, although alprazolam led to changes earlier in treatment, relative to imipramine.

Schweizer, Rickels, Weiss, and Zavodnick (1993) randomly assigned 106 patients with DSM-III diagnoses of PD or agoraphobia with panic attacks (diagnosed with structured interviews) to eight weeks of active treatment with imipramine (mean dosage 175 mg/day), alprazolam (5.7 mg/day), or placebo. In addition, those who improved were assigned to an additional six months of maintenance treatment, which was completed by 27 patients taking alprazolam, 11 taking imipramine, and 10 taking placebo. Alprazolam was more effective than imipramine and placebo for completer analyses on a variety of measures (e.g., attrition, panic frequency,

phobic symptoms) in the acute treatment phase. Imipramine was more effective than placebo on several measures, especially when end-point analyses were considered. During the maintenance phase, patients maintained their panic-free status and no group differences emerged for most measures.

The 48 patients who completed the entire eight-month course of treatment underwent a gradual taper from their medications over the course of four weeks (Rickels, Schweizer, Weiss, and Zavodnick, 1993). Although significant withdrawal symptoms were observed in almost all patients discontinued from alprazolam, imipramine and placebo discontinuation tended not to lead to significant withdrawal symptoms. In addition, 33% of patients taking alprazolam were unable to remain medication-free for three weeks, compared to none in the other groups. Three to five weeks after the taper, 35% of patients who successfully discontinued alprazolam reported persistent panic attacks, compared to 18% of patients taking imipramine and 30% of patients taking placebo. Group differences in relapse rates following taper were not significant. At one-year follow-up interviews with completers and dropouts, there were no treatment group differences with respect to additional treatment sought or panic remission, although patients who had completed the eight-month study had a higher remission rate (85%) than dropouts (55%). Therefore, the authors suggest that over the long term, patients who originally received imipramine or placebo did as well at follow-up as patients treated with alprazolam, and without the physical dependence and discontinuation that any long-term alprazolam usage entails.

In a double-blind study of patients meeting DSM-III criteria for PD and PDA (according to structured interviews), Uhlenhuth, Matuzas, Glass, and Easton (1989) randomly assigned 81 patients to eight weeks of treatment with fixed dosages of alprazolam (2 mg/day or 6 mg/day), imipramine (225 mg/day) or placebo. Although 86% of the patients receiving 6 mg/day of alprazolam completed treatment, only 50% of patients in the imipramine group completed week eight. In analyses of end-point data, patients taking 6 mg/day of alprazolam improved significantly more than patients taking placebo on five outcome criteria, including measures of panic frequency, general anxiety, and depression. Compared to placebo, the other active conditions led to greater improvement, but on fewer measures than did 6 mg/day of alprazolam. Overall, 6 mg/day of alprazolam was the most

effective treatment, with 76% of patients reporting no major panic attacks at week eight, compared to 30%, 55%, and 50% in the placebo, alprazolam (2 mg/day), and imipramine groups, respectively.

Charney et al. (1986) treated 71 patients meeting DSM-III criteria for PD with eight weeks of imipramine (mean dose at week eight = 141 mg/day), alprazolam (mean dose = 3.1 mg/day), or trazodone (mean dose = 250 mg/day) following three weeks on placebo. Findings from this study were similar to those reported in other studies. Imipramine and alprazolam led to improvement on a variety of measures, although the effects of alprazolam were evident earlier in treatment. Trazodone was not found to be especially helpful.

Finally, Woods et al. (1992) investigated the effects of combining alprazolam and imipramine. Forty-eight patients meeting DSM-III-R criteria for PD (by structured interview) were randomly assigned to receive imipramine plus alprazolam or imipramine plus placebo for four to six weeks, followed by a two-week taper of the alprazolam or placebo and two additional weeks of treatment by imipramine alone. Patients taking alprazolam and imipramine responded faster to treatment, but had a more difficult time during the discontinuation phase, compared to patients taking imipramine and placebo.

Other Comparative Medication Studies

Alprazolam Studies

Tesar et al. (1987) compared alprazolam (mean dosage 5.2 mg/day), clonazepam (mean dosage 2.4 mg/day), and placebo in a six-week double-blind study of 44 patients who met DSM-III-R criteria for PD or PDA by structured interview. On measures of panic, anticipatory anxiety, and phobic symptoms, patients in the active treatment groups did significantly better than patients taking placebo and there were no significant differences in the efficacy of alprazolam and clonazepam.

In a double-blind study comparing lorazepam (mean dosage = 7 mg/day) and alprazolam (mean dosage = 3 mg/day), Schweizer et al. (1990) treated 67 patients meeting DSM-III criteria for PD or PDA for

six weeks, following a one-week placebo washout. Both groups showed significant improvement in the first week of treatment and maintained their gains throughout the study. By the end of treatment, 50% of patients taking lorazepam and 52% of those taking alprazolam reported complete remission of panic attacks.

Ravaris, Friedman, Hauri, and McHugo (1991) randomly assigned 29 patients with DSM-III diagnoses of PD or PDA (by structured interview) to be treated by alprazolam (mean dosage of 5.0 mg/day) or propranolol (mean dosage = 182 mg/day). Both treatments decreased panic frequency and phobic symptoms. Although alprazolam worked more quickly, there were no differences between the two drugs by the end of treatment.

Finally, Sheehan, Raj, Harnett-Sheehan, Soto, and Knapp (1993) compared alprazolam (mean dose = 5.2 mg/day), high dose buspirone (mean dose = 61 mg/day) and placebo in 85 patients who completed eight weeks of double-blind treatment. On measures of panic, anxiety, phobic symptoms, and disability, alprazolam was significantly more effective than buspirone, which did not differ from placebo on any outcome measures.

Other Medication Studies

Pohl, Balon, Yeragani, and Gershon (1989) treated 60 patients meeting DSM-III criteria for PD or PDA with imipramine (mean dose 140 mg/day), buspirone (mean dose 29.5 mg/day) or placebo for eight weeks. All patients initially received four to seven days of single-blind placebo. Patients were evaluated at a screen visit, at a baseline visit following four to seven days of placebo, at weekly intervals for the first four weeks, and at bi-weekly intervals for the last four weeks of the study. Data for patients evaluated at each visit indicated that buspirone and imipramine were significantly better than placebo on measures of panic frequency, anxiety, and global psychopathology. However, at the end of the study, there were no significant differences in improvement among the three groups. The authors cite the relatively high rate of dropouts (only 10 to 11 patients completed treatment in each group), and the lower mean dose of imipramine in this study than in other controlled studies, as possible limitations to this study.

Feet and Götestam (1994) compared 12 weeks of treatment with clomipramine plus dicyprazine or clomipramine plus placebo. Mean dosage of

clomipramine was similar in the two groups (126 mg/day in the dicyprazine group and 130 mg/day in the placebo group). Forty-five patients meeting DSM-III-R criteria for PD or PDA (according to a structured interview) participated in the study. Although both treatment groups experienced improvement, combined treatment led to a greater response on a variety of measures as well as fewer side effects than clomipramine monotherapy. Furthermore, patients in the combined treatment group had higher serum levels of clomipramine and its metabolites than did patients in the clomipramine only group, despite similar dosages of clomipramine.

Finally, Slaap, van Vliet, Westenberg, and den Boer (1995) investigated predictors of non-response in a study comparing 12 weeks of treatment with fluvoxamine and brofaromine in 44 patients meeting DSM-III-R criteria for PD or PDA. For the 32.6% of patients who were classified as non-responders, scores tended to be higher on measures of phobic avoidance, relative to responders.

Summary

A variety of medications have been shown to be more effective than placebo for treating PD and PDA, including benzodiazepines (e.g., alprazolam, clonazepam, adinazolam, lorazepam), tricyclic antidepressants (e.g., imipramine), and SSRI antidepressants (e.g., clomipramine). Other medications (e.g., CCK_b antagonists, buspirone, propranolol) have not been found to be especially helpful for patients with PD or PDA. Among medications that have been shown to be effective, there are few differences in efficacy. Studies suggest, however, that over the long-term, individuals treated with imipramine or placebo do equally well as patients treated with alprazolam, and without the withdrawal side effects of alprazolam. Most individuals with PD have difficulty discontinuing treatment with the benzodiazepines, even with gradual tapering of the medication. In light of this, investigators have begun to develop specific programs to help patients stop taking anxiolytics, including use of cognitive-behavioural therapy.

Studies of Psychological Interventions

Because there are no controlled studies of traditional psychotherapies for PD and PDA, this section focuses exclusively on studies involving cognitive and behavioural therapies (CBT). Cognitive and behavioural strategies that have been used in the treatment of PD include cognitive restructuring, breathing retraining, applied relaxation, and interoceptive exposure. In addition, *in vivo* exposure has been studied extensively for patients with agoraphobic avoidance.

Cognitive-Behavioural Therapy vs. No Treatment or an Alternative Treatment

Telch et al. (1993) randomly assigned 67 patients with PD or PDA diagnoses (based on structured interviews) to group treatment with CBT (including education, cognitive therapy, breathing retraining, and interoceptive exposure) or a delayed treatment control condition. Following eight-weeks of treatment, 85% of patients receiving CBT were panic-free, compared to 30% of individuals in the control condition. Recovery (i.e., attainment of normal levels of functioning with respect to panic attacks, anxiety, and avoidance) was achieved by 64% of the treated group and 9% of the delayed treatment group. In a subsequent report based on a larger sample of patients in this study (N = 156), Telch, Jaimez, Jacquin, and Harrington (1995) found that treated patients showed significantly greater reduction in functional impairment and improved quality of life, relative to those in the control condition. Furthermore, anxiety and phobic avoidance had a significant impact on quality of life, but panic attack frequency did not. These authors suggest that the short-term nature of panic attacks may lead to less impairment than the more chronic and pervasive symptoms of anxiety and phobic avoidance.

In the only study ever to investigate CBT as an early intervention for panic attacks (and perhaps a method of preventing the onset of PD), Swinson, Soulios, Cox, and Kuch (1992) randomly assigned 33 patients presenting to the emergency room with DSM-III-R panic attacks to one of two treatment conditions: (1) reassurance; or (2) reassurance plus exposure instructions. Each intervention was provided in a single 60-minute session. Assessments were conducted at baseline, three-months, and six-months following the session. Patients receiving reassurance only were significantly more depressed (but still not clinically

depressed, on average) and reported more panic attacks at six-month follow-up than individuals who received exposure instructions, despite a lack of differences at baseline. In addition, patients receiving exposure instructions improved over time on all measures (including measures of agoraphobic avoidance), whereas those receiving reassurance only did not improve on any measures.

Three studies have recently compared CBT to supportive psychotherapy for PD. In the first study (Beck, Sokol, Clark, Berchick, and Wright, 1992) 33 patients meeting DSM-III criteria for PD (by structured interview) were randomly assigned to 12 weeks of focused cognitive therapy or eight weeks of supportive psychotherapy (client-centered) followed by an opportunity to receive an additional 12 weeks of cognitive therapy. After the initial eight weeks of treatment, cognitive therapy had led to greater reductions in panic symptoms (71% panic free) and generalized anxiety, compared to the group receiving supportive psychotherapy (25% panic free). After eight weeks, 94% of the patients in the psychotherapy group chose to receive 12 additional sessions of cognitive therapy. At one-year follow-up, 87% of the cognitive therapy-only group and 79% of those who received supportive psychotherapy followed by cognitive therapy remained panic-free.

By contrast, Shear, Pilkonis, Cloitre, and Leon (1994) found no differences between CBT (breathing retraining, muscle relaxation, cognitive therapy, interoceptive and in vivo exposure) and a non-prescriptive treatment (reflective listening to patients discussing their life problems and stresses). Treatment lasted 15 weeks and all patients met DSM-III-R criteria for PD or PDA, according to structured interviews. Both treatments were effective on a variety of measures and groups did not differ in their response to treatment. At six-month follow-up, 75% of those receiving CBT and 68% of those in the psychotherapy group were panic-free.

Finally, Craske, Maidenberg, and Bystritsky (1995) treated 30 patients with DSM-III-R diagnoses of PD or PDA with four sessions of CBT or non-directive therapy before entering a placebo-controlled pharmacological study. In just four sessions, CBT led to significant reductions in worry about panic

and phobic symptoms, whereas non-directive therapy did not. Fifty-three percent of patients in the CBT group and 23% of patients in the psychotherapy group were panic-free after four sessions of treatment, although this difference was not significant. After four sessions of CBT, 38% of patients no longer met entry criteria for panic disorder. Craske et al. theorize that their study may have yielded findings similar to Shear et al. (1994) (above) if patients in the Craske et al. study had been exposed to treatment of a longer duration (e.g., 15 weeks).

Studies Comparing Various Methods of Delivering CBT

Studies Comparing Different Components of CBT

This section reviews studies in which the various components of CBT are compared for patients with PDA and PD. These treatments include cognitive therapy, interoceptive and in vivo exposure, breathing retraining, progressive muscle relaxation, and applied relaxation training (involving a combination of relaxation training and exposure to progressively more difficult situations).

In one of the earliest studies of this type, Mavissakalian, Michelson, Greenwald, Kornblith, and Greenwald (1983) compared 12 sessions of paradoxical intention (i.e., instructions to purposely increase anxiety in phobic situations) and self-statement training (a cognitive coping strategy) for 26 patients with DSM-III diagnoses of agoraphobia. Both groups improved significantly during treatment. Although scores on several agoraphobia measures improved more for patients receiving paradoxical intention than for self-statement training, differences were no longer significant at six-month follow-up.

In a follow-up study, Michelson and colleagues (Michelson, 1986; Michelson, Mavissakalian, and Marchione, 1985, 1988; Michelson, Mavissakalian, Marchione, Dancu, and Greenwald, 1986) treated 88 patients with severe agoraphobia with panic attacks (DSM-III criteria) with one of three methods: (1) paradoxical intention; (2) graduated exposure; and (3) progressive muscle relaxation. In addition, all patients received instructions to conduct self-exposure and programmed practice. Treatment was conducted in twelve two-hour weekly sessions. Patients in all three groups

improved significantly on all major dependent measures (e.g., agoraphobia severity, panic, anxiety, and depression, etc.). Few significant differences among treatments emerged (possibly due to the effects of self-exposure, which was a part of each treatment). Percentages of patients considered to have improved at three-month follow-up were 70.6% for paradoxical intention, 70.0% for graduated exposure, and 71.4% for relaxation training. In general, subjects assigned to treatments that were concordant with their symptoms (i.e., patients who were primarily behavioural responders who received exposure, cognitive responders who received paradoxical intention, and physiological responders who received relaxation training) improved more than individuals who received a treatment that was discordant.

In a similar study, Öst, Westling, and Hellström (1993) compared 12 weekly sessions of applied relaxation, exposure in-vivo, and cognitive therapy for 45 patients meeting DSM-III-R criteria for PDA (by structured interview). In addition to their primary treatment, all participants received self-exposure instructions. All three treatments led to significant improvement on major outcome measures and improvements were maintained at follow-up. Although applied relaxation was more effective than cognitive therapy on two measures, treatments did not differ overall in effectiveness (possibly due to the effects of self-exposure instructions received by both groups). The percentages of patients meeting criteria for clinically significant improvement at one year follow-up were 85% for relaxation, 79% for exposure, and 67% for cognitive therapy.

Beck, Stanley, Baldwin, Deagle, and Averill (1994) compared cognitive therapy, relaxation training, and no formal treatment in 64 patients with DSM-III-R diagnoses of PD and PDA (diagnosed by structured interview). Treatment was conducted in 10 group sessions. Anti-exposure instructions (i.e., instructions not to engage in exposure to feared objects or situations) were given to all participants for the first five sessions, after which anti-exposure instructions were lifted, although no explicit exposure instructions were provided. Overall, cognitive therapy and relaxation training were each superior to “no treatment” on measures of panic,

global functioning, and agoraphobic and associated fears. The percentages of patients classified as responders were 82%, 68%, and 36% for cognitive therapy, relaxation training, and no treatment, respectively. Overall, there were few differences between the two active treatments, although cognitive therapy led to slightly more reduction in agoraphobic fears.

Breathing retraining plus cognitive restructuring, in vivo self-exposure, and a combination of both were compared in an eight-week treatment study with 49 individuals meeting DSM-III-R criteria for PDA according to structured interviews (De Ruiter, Rijken, Garssen, and Kraaimaat, 1989). All three treatments led to significant improvements of each outcome measure except panic frequency, which did not change significantly following treatment. In addition, there were no significant differences between groups. At 18-month follow-up, results were essentially the same and further improvement during the follow-up phase tended to be associated with receiving additional treatment during that time (Rijken, Kraaimaat, de Ruiter, and Garssen, 1992).

van den Hout, Arntz, and Hoekstra (1994) randomly assigned 24 patients with DSM-III-R diagnoses of PDA (with at least moderate levels of agoraphobia) to one of two conditions: (1) four sessions of cognitive therapy followed by eight sessions of cognitive therapy plus exposure; (2) four sessions of supportive psychotherapy followed by eight sessions of exposure. In the initial four sessions, cognitive therapy, but not supportive psychotherapy, led to significant decreases in panic frequency. However, depression, anxiety, and avoidance were not affected during the initial four sessions. The addition of exposure led to changes in each of these parameters with no differences between groups. In other words, cognitive therapy did not improve upon the effects of exposure.

Hoffart (1995) treated 52 patients with DSM-III-R diagnoses of PDA (confirmed by structured interviews) and at least moderate agoraphobic avoidance in a six-week inpatient group program. Patients received either cognitive therapy (including interoceptive exposure) or guided mastery therapy (involving elements of in vivo exposure as well as teaching patients to behave less defensively in feared situations). Overall, both groups improved during treatment and there were few significant differences between groups. More patients in the cognitive therapy group reached high end-state

functioning than in the guided mastery group (39% and 13%, respectively), whereas the percentage of patients considered to be responders did not differ (57% and 35%, respectively). Unfortunately, few details were provided regarding the specific content of each treatment (e.g., amount of exposure and cognitive strategies), making it difficult to interpret the results of this study.

Three studies have compared various CBT strategies in patients without significant agoraphobic avoidance. Barlow, Craske, Cerny, and Klosko (1989) compared 15 weekly sessions of cognitive therapy plus interoceptive exposure, relaxation training, the combination of these treatments, and a wait-list control condition in a study of 60 individuals with DSM-III-R diagnoses of PD without agoraphobia (according to structured interviews). Participants in all three treatment groups improved significantly more than individuals in the wait-list condition. Percentages of individuals who were classified as responders, using composite criteria, were 17% (wait-list), 83% (relaxation), 58% (combined), and 62% (cognitive plus exposure). Forty-six to 50% of each active treatment group and 0% of the wait-list group met criteria for high end-state status. Relaxation training led to the greatest reductions in generalized anxiety, but was associated with a higher dropout rate than the other groups. The conditions that included cognitive therapy and exposure led to the highest percentage of patients (over 85%) reporting no panic attacks following treatment. At two-year follow-up (Craske, Brown, and Barlow, 1991), patients in the relaxation group were doing significantly worse on measures of panic and general psychopathology, compared to the other groups. In contrast, patients in the cognitive therapy plus exposure group tended to maintain their gains or continue to improve. Eighty-one percent of patients in this group (including treatment dropouts) remained panic-free at 24-month follow-up, compared to 42.9% of those in the combined condition and 35.7% of those in the relaxation condition.

Öst and Westling (1995) compared applied relaxation and cognitive therapy (including behavioural experiments) delivered in 12 weekly sessions to 38 patients meeting DSM-III-R criteria for PD with no more than mild agoraphobia

(according to structured interviews). Both groups showed significant gains that were maintained or improved upon at one-year follow-up. Groups did not differ on any measure. Sixty-five and 74% of patients were panic-free following treatment in the applied relaxation and cognitive therapy groups, respectively. At one year follow-up these percentages increased to 82% and 89%, respectively. In addition, both treatments led to lasting improvements in generalized anxiety, depression, and cognitive misinterpretations (of the physical symptoms of panic attacks).

In a similar study, Arntz and van den Hout (1996) compared 12 weekly sessions of applied relaxation, cognitive therapy (including behavioural experiments), and wait-list in 54 patients with DSM-III-R diagnoses of PD with no more than mild agoraphobia (according to structured interviews). Participants completed panic diaries, as well as the Fear of Fear questionnaire (van den Hout, van der Molen, Griez, and Lousberg, 1987), the Dutch version of Spielberger's State Anxiety Inventory (STAI) (van der Ploeg, Defares and Spielberger, 1980), and the Depressive Symptoms Inventory (DSI) (Bouman, 1987). The Symptom Checklist (SCL-90) was used to measure psychopathological complaints (Arrindell and Ettema, 1981).

Active treatment was superior to wait-list on all measures. In addition, cognitive therapy was superior to applied relaxation in reducing panic and questionnaire measures of anxiety, depression, and avoidance. At six-month follow-up, cognitive therapy continued to be superior to applied relaxation on panic measures, but not on questionnaire measures. Following treatment, 27.7%, 50%, and 77.8% of patients were panic-free in the wait-list, relaxation, and cognitive therapy conditions, respectively. These findings were maintained during follow-up.

Spouse-Aided Treatment for PDA

Two studies have examined the effects of including spouses in the cognitive-behavioural treatment of PDA. Barlow, O'Brien, and Last (1984) treated 28 women meeting DSM-III criteria for agoraphobia (according to a structured interview) using 12 sessions of self-initiated in vivo exposure and cognitive restructuring conducted in groups. After their spouses agreed to participate in treatment, patients were randomly assigned to receive treatment in the presence of their spouses or without

spouses. Patients treated with spouses showed significantly more improvement on measures of agoraphobia than patients treated without spouses. Groups did not differ at post-treatment on ratings of general functioning, although those in the spouse condition improved more quickly. Eighty-six percent and 43% of patients were considered responders in the spouse and non-spouse conditions, respectively.

During a two-year follow-up period (Cerny, Barlow, Craske, and Himadi, 1987), patients in the spouse group continued to make gains, whereas those who were treated without spouses did not show continued improvement, especially in the first year. Those treated with spouses showed less functional impairment during the first year after treatment than those treated without spouses, although there were no group differences on measures of general psychopathology. Finally, marital satisfaction improved in both groups and was correlated with improvements in phobic symptoms. In a follow-up article, Craske, Burton, and Barlow (1989) reported that treatment responders were more likely than non-responders to rate themselves and their partners as more communicative, to experience more anxiety reduction during exposure practices, and to report more communication with their spouses at the mid-treatment assessment.

In a similar study, Emmelkamp et al. (1992) compared six sessions (in four weeks) of spouse-aided exposure to exposure without spouses in 60 patients with DSM-III diagnoses of agoraphobia. Both treatments were equally effective and resulted in improvement in agoraphobic symptoms regardless of marital quality. No measures of panic were reported.

Graded vs. Ungraded Exposure for Agoraphobia

Fiengenbaum (1988) treated 48 patients meeting DSM-III criteria for agoraphobia with panic attacks using massed exposure (over six to 10 days) conducted either in a graded or ungraded manner. Before exposure, all participants were provided with detailed assessments (diagnostic phase; four to eight hours) and a comprehensive rationale for treatment (cognitive preparation phase; four to eight hours). Following intensive treatment, all patients continued exposure on their own for six to eight weeks. The massed exposure consisted of a variety of challenging exercises including confinement to a dark, narrow room, flying in small planes, overnight train rides, underground travel, cable cars, shopping, and other activities. In the graded condition, activities were practised in order of difficulty. For the ungraded condition, activities were not practised in any order of difficulty. Overall, ungraded exposure led to significantly greater improvements at five-year follow-up. Whereas 76% of those in the ungraded exposure group reported being symptom-free, only 34.8% of those in the graded exposure group were symptom-free at follow-up. The superiority of ungraded exposure for agoraphobic symptoms was confirmed by patient ratings of agoraphobic fears as well as the percentage of patients in each group who completed a behavioural test at five-year follow-up. It should be emphasized that both groups were treated over a very brief period, such that the course of exposure would not be considered especially gradual, even for the graded exposure group.

Expectancy and Exposure in Agoraphobia

In a study of 32 patients with DSM-III diagnoses of agoraphobia, Southworth and Kirsch (1988) investigated the role of expectancy in reducing fear during 10 exposure sessions conducted over a two to three week period. In the high-expectancy condition ($n = 10$), participants were told they were to receive a proven treatment for agoraphobia. Participants in the low-expectancy condition ($n = 10$) were told that the exposure was part of an assessment procedure and that treatment would begin after the 10 sessions of exposure. In addition, 12 of the participants were assigned to a wait-list control condition. Both treatment groups showed significant improvement from pre- to post-treatment, whereas participants on the wait-list did not improve significantly. However, those in the

high-expectancy group improved more rapidly and to a greater extent on behavioural measures (but not fear measures) than subjects in the low-expectancy group. Group differences did not appear to be related to the amount of exposure that participants in each group received.

Distraction and Exposure in Agoraphobia

Craske, Street and Barlow (1989) reported on an 11-session group treatment study involving in vivo exposure. Individuals meeting DSM-III-R criteria for PDA (according to structured interviews) were separated into two groups. One group was instructed to focus upon internal sensations (focused exposure), the other to engage in distracting tasks (distracted exposure). Although the groups did not differ significantly on individual measures, there was a slight tendency for distracted exposure to lead to more improvement than focused exposure on composite outcome criteria. However, focused exposure was slightly more effective than distracted exposure at six-month follow-up.

Self-Help Treatments and Treatments with Minimal Therapist Contact

Most published studies of self-help treatments have come from Isaac Marks' group in the United Kingdom and from Robert Gould and colleagues in Boston in the United States. Isaac Marks and colleagues have conducted several studies demonstrating the effectiveness of treatments using self-help books and computers. However, most of these studies did not meet criteria for this review due to diagnostically mixed samples. An exception was a study by Ghosh and Marks (1987) in which 40 patients with DSM-III diagnoses of agoraphobia were randomly assigned to receive self-exposure instructions from a psychiatrist, a self-help book, or a computer. All three groups remained significantly improved at six-month follow-up, with no significant differences between them.

Two Canadian groups (Coté, Gauthier, Laberge, Cormier, and Plamondon, 1994; Swinson, Fergus, Cox, and Wickwire, 1995) have recently begun to study these treatments. Swinson et al. (1995) studied the efficacy of an eight-session telephone-

administered behaviour therapy program for individuals with DSM-III-R diagnoses of PDA (diagnosed by telephone-administered structured interviews). Forty-two participants living in rural Ontario, without access to specialized treatment centres, were randomly assigned to receive exposure-based behaviour therapy or were assigned to a wait-list control condition. Patients in the active treatment improved significantly more than patients on the wait-list on agoraphobia-relevant measures (e.g., measures of phobic anxiety, and anxiety sensitivity), but not on measures of general psychopathology. After subsequent treatment, participants originally on the wait-list improved significantly on all measures. Results were maintained at six-month follow-up. This study did not include measures of panic frequency.

Coté et al. (1994) compared therapist-directed treatment (17 weekly sessions) to treatment with reduced therapist contact (seven therapist sessions and seven brief telephone contacts) for 21 patients who met DSM-III-R criteria for PD or PDA. Treatment included information about panic and anxiety, cognitive restructuring, breathing retraining, coping self-statements, interoceptive exposure, and in vivo exposure. Both treatments led to significant improvement with few significant differences between conditions. In each group, at least 73% of patients were panic-free and clinically improved at six-month follow-up.

In a preliminary study, Gould, Clum, and Shapiro (1993) compared eight sessions of standard individual CBT for panic disorder (e.g., cognitive restructuring, breathing retraining, exposure), to bibliotherapy (described as a form of self-help treatment using a self-help manual), and to a wait-list control condition. Thirty-one participants met DSM-III-R criteria for PD with mild agoraphobia according to structured interviews. On a variety of measures, participants in the bibliotherapy group were significantly more improved than those on the wait-list, and did not differ from those in the CBT (therapist-treated) group on most measures. Percentages of patients who were panic-free following treatment were 36%, 73%, and 56% in the wait-list, bibliotherapy, and CBT conditions, respectively.

In a replication study (Lidren et al., 1994), participants meeting DSM-III-R criteria for PD (according to structured interview) were assigned to eight-weeks of CBT in groups, bibliotherapy, or wait-list. Results were comparable to those in the original study by Gould et al.

(1993), with bibliotherapy being equally effective and better than the wait-list group. Improvement was evident on measures of panic frequency, severity of panic, catastrophic cognitions, avoidance, and depression. Improvements were maintained through the six-month follow-up period.

In another replication study, Gould and Clum (1995) compared a self-help treatment to a wait-list control condition in 25 patients with DSM-III-R diagnoses of PD or PDA (according to structured interviews). The self-help treatment involved reading a self-help book on panic disorders, watching a 15-minute informational video that provided information on diaphragmatic breathing, and being provided with a progressive muscle relaxation tape. The self-help treatment was more effective than wait-list for measures of panic frequency, phobic avoidance, and catastrophic cognitions. At two-month follow-up, 69% of patients in the self-help condition and 25% of those on the wait-list were considered improved.

Predictors of Outcome following CBT

A variety of studies have examined specific variables that predict outcome following cognitive and behavioural treatment for PD and PDA. Variables found to predict poorer outcome include poor initial work and social adjustment (Arrindell, Emmelkamp, and Sanderman, 1986), higher pre-treatment severity (Brown and Barlow, 1995), use of medication (Brown and Barlow, 1995; de Beurs, Lange, van Dyck, and Koele, 1995), longer duration of the disorder (de Beurs et al., 1995), high levels of agoraphobic avoidance (de Beurs, van Balkom, Lange, and van Dyck, 1995; Keijsers, Hoogduin, and Schaap, 1994) and agoraphobic cognitions (Keijsers et al., 1994), less time spent on homework (Edelman and Chambless, 1993), higher levels of depression and personality psychopathology (Keijsers et al., 1994), poor motivation for treatment (Keijsers et al., 1994), and therapists who are perceived as less caring, self-confident, and involved (Williams and Chambless, 1990).

Summary

Although numerous studies have shown that CBT is more effective than no treatment for PD and PDA, there appear to be few consistent differences in the

efficacy of the various CBT strategies (e.g., exposure, cognitive therapy, et cetera). However, some studies show that relaxation may be somewhat less effective than other techniques. Inclusion of spouses in CBT treatments may also enhance the effectiveness of CBT. Finally, self-help approaches with minimal therapist contact appear to be effective methods for treating PD and PDA.

Studies Comparing CBT and Medication

Although numerous studies have compared CBT to pharmacological treatments, most included a combined treatment condition and are reviewed in the next section. This section includes only studies in which CBT alone and medication alone were compared to one another (without a combined treatment condition).

Two studies have evaluated the use of CBT or medications in patients who failed to respond to the other treatment. Pollack, Otto, Kaspi, Hammerness, and Rosenbaum (1994) provided 12 weeks of CBT to 15 patients with DSM-III-R diagnoses of PD (confirmed by structured interviews) who had previously failed to respond to treatment with pharmacotherapy, including benzodiazepines (all patients) and antidepressants (one patient). Seven of the patients were judged to have had an adequate trial of medication before beginning CBT, whereas eight were judged to have had an inadequate trial. Overall, CBT led to significant improvements in global functioning and panic frequency.

In a related study, Hoffart et al. (1993) investigated the efficacy of a 12-week trial of clomipramine (up to 150 mg/day) in a group of 18 patients with DSM-III-R diagnoses of PDA (diagnosed with structured interviews) who had previously failed to respond to behaviour therapy. On most outcome measures, patients improved following treatment with clomipramine, although gains were modest.

Three controlled studies have compared medication treatments to CBT. Klosko, Barlow, Tassinari, and Cerny (1990) compared 15 weeks of CBT, alprazolam (mean dosage = 4.6 mg/day), placebo and wait-list for 57 patients with DSM-III diagnoses of PD (diagnosed by structured interviews). On measures of panic frequency, generalized anxiety and global improvement, CBT was superior to placebo, whereas alprazolam did not differ

from placebo or CBT. Percentages of patients who were panic-free following treatment were 87% for CBT, 50% for alprazolam, 36% for placebo, and 33% for wait-list.

Black, Wesner, Bowers, and Gabel (1993) compared fluvoxamine (mean dosage = 230 mg/day), cognitive therapy (without exposure), and placebo in an eight-week study of 75 patients meeting DSM-III-R diagnoses of PD or PDA (diagnosed by structured interviews). Patients taking fluvoxamine improved more than patients taking placebo, whereas patients receiving cognitive therapy did not improve more than those on placebo on most measures. Fluvoxamine led to more improvement than cognitive therapy on many measures, and cognitive therapy was not superior to fluvoxamine on any measures. Following treatment, the percentages of completers who were free of panic were 81%, 53.3%, and 29.4% for patients receiving fluvoxamine, cognitive therapy, and placebo, respectively. Percentages were slightly lower for endpoint analyses. Predictors of positive outcome with fluvoxamine included a low panic attack severity score and the absence of personality disorders. For cognitive therapy, comorbid personality disorders predicted poorer outcome (Black, Wesner, Gabel, Bowers, and Monahan, 1994).

Finally, Clark et al. (1994) compared cognitive therapy, applied relaxation, imipramine (mean dosage = 233 mg/day), and wait-list (followed by active treatment) for the treatment of 64 patients with DSM-III-R diagnoses of PD with no more than moderate agoraphobic avoidance. Treatment included up to 12 sessions in the first three months and up to three booster sessions in the next three months. Patients taking imipramine were tapered off the medication after six months. All groups received self-exposure homework instructions. All three treatments were more effective than wait-list. However, at three months, cognitive therapy was superior to imipramine and applied relaxation on most measures. At six months, there were no differences between cognitive therapy and imipramine and both were superior to applied relaxation on a variety of measures. During follow-up, several patients taking imipramine relapsed so that by 15 months, cognitive therapy was once again

superior to imipramine and applied relaxation on several measures. At 15-month follow-up, the percentages of patients who were panic-free were 85%, 60%, and 47% for cognitive therapy, imipramine, and applied relaxation, respectively. The percentages of patients from each of these groups who relapsed or required more treatment during the follow-up were 5%, 40%, and 26%, respectively.

Studies Investigating Combined CBT and Medications

Imipramine and CBT

Five controlled studies have compared the individual and combined effects of treatment with imipramine and CBT for PDA. Each of these studies was based on individuals who met DSM-III criteria for agoraphobia, although none used structured interviews to confirm the diagnoses.

Marks et al. (1983) treated 45 patients in one of four conditions: (1) imipramine plus therapist-assisted exposure; (2) imipramine plus therapist-assisted relaxation training; (3) placebo plus therapist-assisted exposure; and (4) placebo plus therapist-assisted relaxation. Drug/placebo treatment lasted 28 weeks, with a mean imipramine dosage of 110 mg at the end of treatment. Therapist-assisted exposure or relaxation was conducted over six weekly sessions. In addition, all participants received self-exposure homework instructions. Overall, patients improved on all measures (which included measures of phobic symptoms and depressed mood). There were no differences between imipramine and placebo during treatment and through the one-year follow-up period (possibly due to the relatively low dosage of medication). However, therapist-assisted exposure led to significantly more improvement than relaxation, although differences were small (perhaps due to the effects of self-exposure exercises that were assigned to all groups). At two-year follow-up (Cohen, Monteiro, and Marks, 1984) and five-year follow-up (Lelliott, Marks, Monteiro, Tsakiris, and Noshirvani, 1987), participants continued to be improved, although there were no longer significant differences among any of the groups.

Donald Klein and his colleagues (Klein, Zitrin, Woerner, and Ross, 1983; Zitrin, Klein, Woerner, and Ross, 1983; Klein, Ross, and Cohen, 1987) conducted a 26-week

treatment study of 218 patients (of which 130 met criteria for agoraphobia) who were randomly assigned to three conditions: (1) imipramine plus behaviour therapy (including relaxation training, imaginal exposure, in vivo exposure, and assertiveness training); (2) imipramine plus supportive psychotherapy; and (3) behaviour therapy plus placebo. Mean dosage of imipramine for agoraphobic patients was 204 mg/day. Outcome measures included scales for general anxiety, depression, panic, and phobic avoidance. Overall, patients in all groups showed improvement. However, for patients experiencing unexpected panic attacks (i.e., those in the agoraphobia group), imipramine was superior to placebo. Overall, behaviour therapy and supportive psychotherapy were equally effective. Furthermore, Klein et al. (1987) argued that although exposure was useful for decreasing phobic avoidance, it was not an effective treatment for reducing panic frequency.

Mavissakalian and Michelson studied 62 agoraphobic patients treated in four conditions: (1) imipramine plus self-exposure instructions; (2) therapist-assisted exposure plus self-exposure instructions plus placebo; (3) imipramine plus therapist-assisted exposure plus self-exposure instructions; and (4) self-exposure instructions plus placebo (Mavissakalian and Michelson, 1982, 1983a, 1983b, 1986; Michelson and Mavissakalian, 1985). Treatment was conducted over 12 weekly sessions and the mean imipramine dosage was 130 mg/day. Overall, all groups showed significant improvements on all measures. Imipramine led to significantly more improvement in phobic avoidance than placebo, but not on other measures. Therapist-assisted exposure did not lead to significant improvement over and above the effects of self-exposure instructions.

Telch, Agras, Taylor, Roth, and Gallen (1985) treated 37 agoraphobic patients in three conditions: (1) imipramine plus exposure; (2) imipramine plus anti-exposure instructions; and (3) placebo plus exposure. After eight weeks of initial treatment, those in the anti-exposure group were given general instructions to begin confronting feared situations and no further psychological treatment was provided. Medication and placebo were continued for an additional 18 weeks for the other two groups,

respectively. The mean dosage of imipramine at week eight ranged from 183 to 197 mg/day across groups. At week 26, dosages ranged from 179 to 181 mg/day. At week eight, the imipramine plus exposure group was significantly more improved than the other two groups and was the only group to show a reduction in panic attacks. The imipramine plus anti-exposure instructions group showed little improvement in phobic indices, no reduction in panic, but showed significant improvement in anxiety and dysphoric mood. These findings were essentially maintained at week 26, with the imipramine plus exposure group being significantly more improved than the placebo plus exposure group on several measures and the only group to show significant reductions in panic attacks.

Finally, Cox et al. (1988) compared the effects of high (200-250 ng/ml) vs. low (100-150 ng/ml) serum levels of imipramine on 36 patients receiving 12 weekly group sessions of behaviour therapy for agoraphobia (breathing retraining, in vivo exposure). Overall, both groups improved equally, although the only measure given was a measure of general psychopathology (Hopkins Symptom Checklist).

Alprazolam and CBT

Marks et al. (1993) studied 154 patients meeting DSM-III criteria for agoraphobia with panic attacks (diagnosed with structured interviews) in a cross-national randomized trial comparing eight weeks of alprazolam (mean dosage = 5 mg/day), behaviour therapy, and their combination. Specifically, patients were assigned to treatment in one of four conditions: (1) alprazolam plus exposure; (2) alprazolam plus relaxation; (3) placebo plus exposure; and (4) placebo plus relaxation. This study was unique in that all patients were discontinued from their alprazolam and placebo from weeks eight to 16 and underwent a treatment-free follow-up lasting to week 43. All four treatment groups improved on panic measures. By the end of treatment, alprazolam and exposure were both effective on non-panic measures, although exposure had twice the effect size as alprazolam. During taper and follow-up, the gains achieved from alprazolam were lost, whereas gains from exposure were maintained. In addition, although combined therapy improved outcome slightly during treatment, following discontinuation, combined treatment was slightly less effective than exposure alone. By week 43, participants who had received exposure and placebo

had the lowest scores on all measures, although significance tests were only conducted for certain comparisons (e.g., exposure vs. alprazolam).

Several outcome predictors were identified for the above study. Basoglu, Marks, Kiliç, Brewin, and Swinson (1994) found that patients who attributed their improvement to medication (regardless of whether they were taking alprazolam or placebo) were more likely to experience withdrawal symptoms and loss of gains than were patients who attributed their improvements to their own efforts. Pre-treatment predictors of poor outcome at post-treatment included first time psychotropic medication use, more severe agoraphobia, and longer duration of illness. Predictors of poorer long-term outcome included more severe agoraphobic symptoms, older age, past history of depression, and longer duration of illness (Basoglu, Marks, Swinson, et al., 1994).

Riley et al. (1995) tested the hypothesis that alprazolam interferes with the efficacy of CBT. Twenty-four patients with DSM-III-R diagnoses of PD or PDA (diagnosed with structured interviews) were treated with 15 sessions of CBT (including relaxation, cognitive restructuring, in vivo exposure and interoceptive exposure) conducted over eight weeks. In addition, patients were randomly assigned to low dosage (mean = 1.08 mg/day) or moderate dosage (mean = 3.53 mg/day) of alprazolam. Patients completed the Beck Anxiety Inventory (Beck, Epstein, Brown and Steer, 1988), the Fear Questionnaire (Marks and Matthews, 1979), and the Body Sensations and Agoraphobic Cognitions Questionnaires (Chambless, Caputo, Bright and Gallagher, 1984). Patients also completed Panic Diary Cards (Barlow and Cerny, 1988) throughout the study. Independent raters interviewed the patients at the same time points and completed the Hamilton Anxiety and Hamilton Depression Rating Scales (Hamilton, 1959, 1960).

Patients on moderate dosages of medication took longer to achieve peak levels of heart rate during exposure practices but returned to baseline more quickly during exposures than patients on low dosages. The absolute magnitude of these changes did not differ across groups and the physiological changes were not related to treatment outcome.

Eighty-three percent of the total sample were panic-free at week eight and 50% met criteria for high end-state functioning (defined as having no panic attacks during the last week of treatment and a posttest Hamilton Anxiety score of 12 or less).

Other Studies of Medication and CBT

Clomipramine and CBT

Fahy, O'Rourke, Brophy, Schasmann, and Sciascia (1992) treated 79 patients who met DSM-III-R criteria for PD or PDA (diagnosed with structured interviews) with six weeks of clomipramine, lofepramine, or placebo. In addition, all patients received weekly sessions of behaviour therapy. By week six, both drugs were superior to placebo on several measures but not panic frequency. Both medications were equally effective throughout treatment and the six-month follow-up period, although significantly more patients in the clomipramine group dropped out of treatment, presumably due to intolerance of the medication.

Fluvoxamine and CBT

de Beurs, van Balkom, Lange, Koele, and van Dyck (1995) randomly assigned 96 patients with DSM-III-R diagnoses of PDA (confirmed by structured interviews) to four conditions: (1) fluvoxamine (12 weeks, 150 mg/day) plus in vivo exposure introduced after week six; (2) placebo (12 weeks) plus in vivo exposure after week six; (3) panic management (12 sessions of interoceptive exposure and breathing retraining) plus in vivo exposure introduced after week six; and (4) in vivo exposure alone. All four groups improved significantly on measures of agoraphobic avoidance; however, fluvoxamine plus exposure led to more improvement than the other groups, which did not differ from one another. By two-year follow-up, the other groups had caught up to the fluvoxamine plus exposure group and there were no longer differences across groups on measures of agoraphobia, depression, anxiety, and panic (de Beurs, van Balkom, Lange, Koele et al., 1995).

Buspirone and CBT

Cotraux et al. (1995) compared treatment with 16 weeks of buspirone (about 30 mg/day) and placebo in 77 patients with DSM-III-R diagnoses of PDA (confirmed by

structured interviews). In addition, all participants received concurrent treatment with CBT. Both groups improved on measures of agoraphobia, panic, and depression, although buspirone led to greater improvement on measures of depression and generalized anxiety. Outcome was predicted by positive expectations for medication in both groups. By week 68, improvements were maintained, but group differences were no longer present.

Diazepam and CBT

Wardle et al. (1994) examined the effects of concurrent diazepam treatment on exposure therapy for 91 patients meeting DSM-III-R criteria for PDA. After taking diazepam (5 - 15 mg/day) or placebo for four weeks, participants received eight sessions of in vivo exposure in seven weeks. After week 12, exposure and diazepam were discontinued. Both groups improved significantly on a range of measures and maintained their gains following discontinuation of treatment and during the one-year follow-up period. However, the short- and long-term outcome of behavioural treatment was not significantly affected by the addition of concurrent treatment with diazepam.

Paroxetine and CBT

Oehrberg et al. (1995) compared 12 weeks of treatment with paroxetine (20 mg, 40 mg, or 60 mg/day) and placebo in 120 patients meeting DSM-III-R criteria for PD or PDA. All participants received concurrent cognitive therapy. Paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy on two out of three measures of panic frequency. Thirty-six percent of patients on paroxetine and 16% of patients on placebo were panic-free at week 12.

Summary

Overall, there appear to be no consistent differences in the efficacy of CBT, medications, and their combination. In some studies, CBT has been the preferred treatment, whereas in other studies medications appear to be more effective. In most studies, there are few differences among these approaches, especially over the long-term.

Meta-Analytic Studies

Recently, several investigators have conducted meta-analyses of treatments for PD and PDA. Boyer (1994) compared selective serotonin reuptake inhibitor antidepressants (SSRIs; e.g., clomipramine, fluvoxamine, paroxetine, zimeldine) to imipramine in a meta-analysis of drug treatments for PD and PDA. Overall, there was evidence that SSRI's were superior to imipramine, and there were no significant differences between the serotonergic medications. In a meta-analytic study comparing placebo-controlled trials of antidepressants (mean duration 16 weeks) and benzodiazepines (mean duration seven weeks), Wilkinson, Balestrieri, Ruggeri, and Bellantuono (1991) found that active treatment was 25% more successful than placebo over a mean duration of 14 weeks. However, no significant differences were found in short-term treatment of PD between antidepressants and benzodiazepines.

Cox, Endler, Lee, and Swinson (1992) compared imipramine, alprazolam, and in vivo exposure in a meta-analysis of treatments for PDA. Across studies, alprazolam tended to have significant effects on global severity, anxiety, panic frequency and severity, and agoraphobic fear. In contrast, imipramine only effected global severity, anxiety, and depression, but had no significant effects on panic or agoraphobic fears. Exposure had significant effects on all measures, except panic frequency and severity. Overall, exposure had the most consistently large effect sizes.

Finally, Clum, Clum, and Surls (1993) compared psychological and pharmacological treatments in a meta-analysis of studies investigating treatments for PD and PDA. Psychological coping strategies (e.g., relaxation, cognitive therapy, exposure) led to the most consistent strong effect sizes. Flooding (a form of exposure therapy) and combined treatments (i.e., medication and CBT) led to moderate effect sizes. Among pharmacological treatments, antidepressants were the most effective, although differences between effect sizes for antidepressants and other medications were not significant.

General Summary and Conclusions

Among the anxiety disorders, PD and PDA are the most extensively researched. Numerous outcome studies have demonstrated the effectiveness of pharmacological,

psychological, and combined treatments. In addition, compared to the other anxiety disorders, studies of PD and PDA have typically been more sophisticated in their designs and measures. In general, most studies in this chapter used structured diagnostic interviews to select participants. In addition, outcome measures include a broad range of assessments that evaluate changes in panic frequency, generalized anxiety, depression, agoraphobic avoidance and other domains of functioning. Studies often included self-report measures, behavioural measures, clinician-administered measures, and psychophysiological assessments.

In pharmacological trials, a variety of medications have been demonstrated to be more effective than placebo for treating PD and PDA. Although alprazolam and imipramine have been the most frequently researched medications, other drugs that have been shown to be effective include clonazepam, adinazolam, clomipramine, lorazepam, fluvoxamine, and several other medications. In addition, there is evidence with some medications (e.g., imipramine) that longer durations of treatment lead to more favourable long-term outcomes. In general, there were few differences among drugs in terms of efficacy. However, benzodiazepines tended to be associated with earlier improvements and greater rates of relapse following discontinuation, relative to antidepressants. Interestingly, CBT has been shown to help patients to discontinue their medications without relapse.

Numerous studies have demonstrated that CBT is more effective than no treatment. Furthermore, most studies have shown CBT to lead to greater improvements than alternative psychological treatments (e.g., supportive psychotherapy). Although there were few consistent differences across studies in the effectiveness of various CBT strategies (e.g., cognitive therapy, exposure, applied relaxation, etc.), some studies have shown that relaxation is somewhat less effective than other techniques. In addition, several studies have shown CBT to be more effective than pharmacological approaches, particularly over the long-term. Other studies have shown few differences between drug treatments and psychological interventions. In only two studies was pharmacotherapy more effective

than CBT. In general, combined pharmacotherapy and CBT was no more effective than either alone, although there was some evidence that patients who attributed their improvements to medications were at a greater risk for relapse than individuals who attributed their improvement to psychological interventions. Finally, a variety of studies have shown that patients with PD and PDA can benefit from interventions with reduced therapist contact.

A variety of studies have identified predictors of poor outcome following CBT treatment for PD and PDA. These include poor initial work and social adjustment, higher pre-treatment severity, use of medication, longer duration of the disorder, high levels of agoraphobic avoidance and agoraphobic conditions, less time spent on homework, and higher levels of depression and personality psychopathology. Poor motivation for treatment, and therapists who are perceived by patients to be less caring, less self-confident and less involved are also important predictors of poor outcome.

Although the large questions of which treatments work for PD and PDA have essentially been answered, there are still many issues that remain unresolved. For example, although it seems clear that CBT and pharmacotherapy are both effective, it is possible that different patients are more likely to respond to each type of treatment. There are studies showing that individuals who have failed in behaviour therapy can still respond to medications; and that patients who have not responded to pharmacotherapy can still benefit from CBT. We do not yet know how to predict which patients might best respond to CBT and which individuals are more likely to improve with medications.

In addition, little is known about treating PD and PDA in special populations, such as the elderly, adolescents, culturally diverse groups, and individuals with multiple diagnoses (e.g., substance abuse). More research will help to determine the effectiveness of CBT, pharmacological, and combined treatments in diverse populations.

Finally, little is known about the best way to sequence treatments. For example, when offering patients combined treatments, should different treatment components be introduced at different times? Studies of treatment sequencing will help to address this question.

CHAPTER 5

OBSESSIVE-COMPULSIVE DISORDER

Introduction

Numerous studies of biological and psychological treatments have been conducted with individuals with obsessive-compulsive disorder (OCD). The SSRI antidepressants (e.g., clomipramine, sertraline, fluoxetine, fluvoxamine) have been consistently shown to be helpful for alleviating OCD symptoms, whereas the tricyclic antidepressants (e.g., desipramine) appear to be less useful. Studies are now being completed with newer medications such as paroxetine, although results have yet to be published. Several uncontrolled studies suggest that psychosurgery may be an effective treatment for especially severe cases (Mindus and Jenike, 1992).

Among psychological treatments, exposure and response prevention appear to be the treatment of choice, although smaller, uncontrolled studies have examined the use of other strategies (e.g., cognitive therapy) as well. In addition, studies examining self-help treatments for OCD are currently being conducted, although results are not yet published. Preliminary findings from Fritzlner, Losee, and Hecker (1995) suggest that treatment using a self-help book may be effective for some patients. In addition, a study by Baer et al. (1995) suggests that telemedicine may be an effective way of administering assessments for patients with OCD. Future studies will help to determine whether telemedicine and other technological advances (e.g., computer-administered treatments) will be useful in the treatment of OCD.

Medication Studies

Clomipramine is the most studied drug in the treatment of OCD with over 20 controlled clinical trials and numerous uncontrolled studies. However, a variety of other medications have been studied for OCD as well. All studies reviewed in this section

were based on DSM-III (American Psychiatric Association, 1980) or DSM-III-R (American Psychiatric Association, 1987) criteria, although almost none used structured interviews to diagnose OCD. Studies which used structured interviews are highlighted.

Clomipramine vs. Placebo

The largest studies of clomipramine in OCD to date were conducted by the Clomipramine Collaborative Study Group (1991). This project entailed two double-blind trials conducted with 520 patients at 21 different treatment centres. Patients met DSM-III criteria for OCD, although diagnoses were based on unstructured clinical interviews. Because some investigators (e.g., Marks, 1983) have argued that the impact of antidepressant treatments for OCD is mediated by the effects on depression, these studies enrolled patients with no more than mild levels of depression. In both studies, a 10-week trial of clomipramine was significantly more effective than placebo in decreasing OCD symptoms. In study one, patients taking clomipramine (mean dose = 234.5 mg/day) experienced a 38% decrease in scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989), whereas those taking placebo had only a 3% decrease. These results were replicated in study two, with YBOCS scores decreasing 44% and 5% for clomipramine (mean dose = 218.8 mg/day) and placebo, respectively. In addition to its efficacy for decreasing OCD symptomatology, clomipramine was generally well tolerated by patients. Common side effects included dry mouth, dizziness, tremor, fatigue, digestive system problems, and urogenital problems.

The efficacy of clomipramine in OCD has been confirmed in numerous controlled studies. For example, Greist et al. (1990) found that whereas 73% of patients with DSM-III OCD improved with 12 weeks of treatment with clomipramine (mean dose = 255 mg/day), only 12.5% of patients taking placebo showed improvement on the

YBOCS and other measures. Clomipramine was also found to be significantly more effective than placebo in studies by Hoehn-Saric, McLeod, Zimmerli, and Hipsley (1993), Jenike et al. (1989), Katz, DeVeugh-Geiss, and Landau (1990), and Mavissakalian, Jones, Olson, and Perel (1990). Consistent with the hypothesis that clomipramine is effective for decreasing OCD symptoms, Mavissakalian et al. (1990) showed that response to clomipramine was related to plasma levels of the drug. Two placebo-controlled studies have demonstrated the efficacy of clomipramine for children with OCD (Deveugh-Geiss et al., 1992; Flament et al., 1985). In fact, in no controlled study has placebo been found to be as effective as clomipramine in the treatment of OCD.

A number of studies have identified predictors of response to treatment with clomipramine. Ackerman, Greenland, Bystritsky, Morgenstern, and Katz (1994) found that age of onset was a strong predictor of response, with later onsets being associated with a stronger response to treatment. This finding was stable even when age of onset was statistically controlled for length of illness. Low levels of depression were associated with a greater treatment response although the relationship between depression and treatment response was not linear. Finally, higher YBOCS scores were associated with a greater response to treatment. However, this finding was found in patients taking placebo as well, suggesting that it may have been an artifact of regression to the mean. Ravizza, Barzega, Bellino, Bogetto, and Maina (1994) confirmed the finding that later age of onset is associated with greater response to treatment.

Other predictors of positive response included shorter duration of illness, an episodic course, an absence of previous hospitalizations, presence of compulsions, and absence of comorbid schizotypal personality disorder at pre-treatment. Baer et al. (1992) studied the impact of pre-treatment personality disorders on outcome following clomipramine treatment. Although having one personality disorder tended not to affect treatment outcome, the presence of particular disorders (i.e., schizotypal, borderline, and avoidant personality disorders) was predictive of poorer outcome, as was the total number of comorbid personality disorders.

The studies reviewed above investigated only the effects of acute treatment with clomipramine. Only one study could be found that examined the effects of discontinuation from clomipramine (Pato, Zohar-Kadouch, Zohar, and Murphy, 1988). Eighteen patients who had previously improved with five to 27 months of treatment with clomipramine (mean plasma level = 194 ng/ml) were discontinued during a seven-week placebo period. Following discontinuation, almost 90% of patients experienced a substantial recurrence of OCD symptoms, and over 60% experienced a significant increase in depression. The increase in OCD and depressive symptomatology following discontinuation was not related to the duration of previous treatment. These findings suggest that although clomipramine appears to be an effective treatment for OCD, the effects are dependent on patients continuing to use the drug.

Other SSRI Medications vs. Placebo

Double-blind, placebo-controlled studies of OCD treatment have been conducted with a variety of SSRI medications including sertraline, fluoxetine, and fluvoxamine. As with the studies of clomipramine, none of these studies reported having used structured interviews to confirm diagnoses.

Sertraline vs. Placebo

In an eight-week double-blind trial, Chouinard et al. (1990) found that sertraline (mean dose = 180 mg/day) was superior to placebo on almost all measures. Whereas 56% of patients taking sertraline experienced some improvement on a measure of global improvement, 32% of patients taking placebo experienced some improvement on this measure. Greist et al. (1995) treated 324 patients with DSM-III-R diagnoses of OCD in a 12-week trial comparing three fixed dosages of sertraline to placebo. Patients taking sertraline improved more than patients taking placebo on a variety of outcome measures. Furthermore, dosage of sertraline (50 mg/day vs. 100 mg/day vs. 200 mg/day) was not related to overall outcome. Common adverse effects included diarrhea, insomnia, decreased libido, nausea, ejaculation failure, tremor, sweating, and weight gain.

Fluoxetine vs. Placebo

A 13-week, multicenter investigation of 355 patients with DSM-III-R OCD compared three fixed dosages (20 mg/day, 40 mg/day, 60 mg/day) of fluoxetine to placebo (Tollefson et al., 1994). Whereas response rate (i.e., 35% decrease in YBOCS scores) was 8.5% for the placebo group, 32% to 35% of the treatment groups showed improvement, with no significant differences among the three dosage levels. Common side effects experienced by the treatment groups included nausea, dry mouth, and tremors.

Fluvoxamine vs. Placebo

Four double-blind controlled studies have examined the efficacy of fluvoxamine, finding in general that fluvoxamine is superior to placebo for the treatment of OCD. Perse, Greist, Jefferson, Rosenfeld, and Dar (1987) treated 16 patients with DSM-III OCD in a 20-week double-blind crossover trial with fluvoxamine (mean plasma level = 296.85 mg/day) and placebo. Fluvoxamine led to improvement (physician's global rating of at least "somewhat improved") in 81% of patients on fluvoxamine and only 19% of those taking placebo. Goodman, Price, Rasmussen, Delgado, et al. (1989) found that 43% of 21 patients experienced a reduction in OCD symptoms after treatment with fluvoxamine. None of the 21 patients on placebo were much improved, as reflected by scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS).

In a study of 38 patients with OCD, Jenike et al. (1990) found that 10 weeks of treatment with fluvoxamine (mean dosage = 294 mg/day) was significantly better than placebo on two of three measures, including YBOCS ratings. Side effects were mild, with the most common symptoms including insomnia, nausea, fatigue, and headache. Mallya, White, Waternaux, and Quay (1992) studied 28 individuals with DSM-III-R OCD in a 10-week double blind trial comparing fluvoxamine and placebo. Using 35% improvement in YBOCS scores to define

clinical improvement, 43% of patients taking fluvoxamine were considered to be improved, whereas only 7% of the patients in the placebo group were considered to be improved. In a follow-up discontinuation study, Mallya et al. (1992) found that seven of nine patients relapsed within a few days to weeks of discontinuing fluvoxamine.

Comparative Medication Studies

Clomipramine vs. Other Medications

Three controlled studies have shown that clomipramine is a more effective treatment for OCD than tricyclic antidepressants that are less specifically serotonergic in their action. Thorén, Åsberg, Cronholm, Jörnstedt, and Träskman (1980) studied five weeks of treatment with clomipramine, nortriptyline, and placebo and found that only clomipramine was superior to placebo for reducing OCD symptoms. Although Research Diagnostic Criteria (RDC)(Spitzer, Endicott, and Robins, 1978) were not available at the time the study was designed, the authors retrospectively confirmed that patients met RDC criteria for OCD. The therapeutic effects of clomipramine were not maintained after discontinuation. A 12-week double blind trial by Volavka, Neziroglu, and Yaryura-Tobias (1985) found that clomipramine (mean dose = 292.86 mg/day) was somewhat more effective than imipramine (mean dose = 262.5 mg/day), although both drugs led to only modest decreases in symptomatology. Results were complicated by baseline differences between groups. In addition, patient dropouts led to a final sample of only eight participants per group, which likely limited the power to detect stronger differences. Finally, Leonard et al. (1989) used a cross-over design to compare treatment by clomipramine and desipramine in a group of 48 children and adolescents with OCD. Clomipramine was superior to desipramine on most measures.

Two published controlled studies have compared clomipramine to other SSRI medications. Pigott et al. (1990) conducted two comparing fluoxetine and clomipramine in patients with DSM-III-R diagnoses of OCD. In the first study, 11 patients participated in a double-blind crossover study in which 10 weeks of treatment with fluoxetine (mean dose = 75 mg/day)

and 10 weeks of clomipramine (mean dose = 209 mg/day) were about equally effective, although fluoxetine was associated with fewer adverse effects. In the second study, 21 patients who had previously responded to clomipramine were crossed over to fluoxetine in a double-blind fashion following a placebo washout period. Following 10 weeks of treatment with fluoxetine, improvement in OCD symptoms was the same as with clomipramine. For both studies, the four-week drug washout that occurred before the crossover was associated with substantial relapses in OCD and depressive symptomatology. More recently, Freeman et al. (1994) compared clomipramine and fluvoxamine in a 10-week trial with 66 patients diagnosed with OCD according to DSM-III-R criteria. Clomipramine and fluvoxamine were about equally effective, leading to 31% and 33% reduction in YBOCS scores, respectively.

Three additional controlled studies comparing clomipramine to other medications were found. Insel et al. (1983) compared clomipramine (mean dosage = 236 mg/day) to clorgyline in a six-week double-blind crossover study of 24 patients with DSM-III diagnoses of OCD. Clomipramine led to significant improvement in OCD symptoms, whereas clorgyline did not lead to improvement. Vallejo, Olivares, Marcos, Bulbena, and Menchón (1992) treated 30 patients with DSM-III OCD in a 12-week trial comparing clomipramine and phenelzine. OCD symptomatology improved in both groups, with no significant differences in improvement. Finally, in a controlled multiple crossover study, Hewlett, Vinogradov, and Agras (1992) compared three active treatments (i.e., clomipramine, clonazepam, clonidine) and a control medication (diphenhydramine) without hypothesized benefit in OCD. Twenty-eight patients with a DSM-III-R diagnosis of OCD (diagnosed using the Structured Clinical Interview for DSM-III-R, SCID)(Spitzer, Williams, and Gibbon, 1987) were rotated through six-week trials of each medication. Overall, clomipramine and clonazepam were equally effective at decreasing YBOCS scores,

although they appeared to be effective for different patients (40% of patients failing to respond to clomipramine responded to clonazepam). Clonidine did not lead to significant change, whereas the control medication, diphenhydramine led to a decrease in OCD symptoms. Overall, clonazepam led to the most improvement in YBOCS scores in the first three weeks of treatment.

Other Comparative Medication Studies

The only other controlled comparative medication outcome study found was a comparison of fluvoxamine (mean dose = 130 mg/day) and desipramine (126 mg/day) in 40 patients meeting DSM-III-R criteria for OCD (Goodman et al., 1990). This was a double-blind study in which patients received an eight-week trial of one of these two medications. Fluvoxamine was significantly more effective than desipramine at decreasing YBOCS scores. Fifty-two percent of patients on fluvoxamine were considered to be responders, while only 10% of patients in the desipramine group responded to treatment.

Medication Augmentation Studies

Several studies have begun to examine the effects of augmenting traditional drug treatments for OCD with other medications. Two studies found that adding buspirone was no more effective than adding a placebo to treatment of DSM-III-R OCD with fluvoxamine (McDougle et al., 1993) and fluoxetine (Grady et al., 1993), respectively. In contrast, McDougle et al. (1994) found that haloperidol augmentation in fluvoxamine-refractory OCD was more effective than augmentation with a placebo. Of 62 patients treated with fluvoxamine, 34 who were considered to be treatment refractory were given haloperidol or placebo for four weeks. Sixty-five percent were considered to respond to the addition of haloperidol to their fluvoxamine treatment, whereas none responded to the addition of a placebo. Haloperidol augmentation tended to be effective for patients with comorbid tic disorders but not for patients without tic disorders.

In light of research findings that lithium augmentation can improve the response rate to antidepressant medications, two studies have examined the effectiveness of lithium augmentation of treatment with fluvoxamine (McDougle,

Price, Goodman, Charney, and Heninger, 1991) and clomipramine (Pigott et al., 1991), respectively, for patients meeting DSM-III-R criteria for OCD. In neither study was adjunct lithium treatment found to be helpful.

Summary

In general, the SSRI antidepressants appear to be the pharmacological treatment of choice for OCD. Clomipramine has been the most researched medication for OCD, with more than ten controlled studies. Other SSRIs, including sertraline, fluoxetine, and fluvoxamine also appear to be helpful for decreasing OCD symptomatology. There appears to be little difference in the effectiveness of various SSRI medications. Finally, a number of studies have shown that tricyclic antidepressants (e.g., nortriptyline, imipramine) are less effective than clomipramine.

Studies of Psychological Treatments

Numerous studies have examined the efficacy of psychological treatments for OCD. Those found to be efficacious are cognitive-behavioural therapies. Although newer studies have ensured that patients meet DSM-III or DSM-III-R criteria for OCD, many of the original studies establishing the use of behavioural treatments for OCD were conducted in the 1970s, before the publication of DSM-III. As was the case with medication studies of OCD, the vast majority of studies did not use structured interviews to confirm diagnoses of OCD. Studies in which diagnoses were based on structured interviews will be highlighted.

CBT Studies

Foa and Goldstein (1978) studied the efficacy of exposure to feared cues and prevention of compulsive rituals in 21 patients with OCD. The program consisted of a two-week "information gathering" period during which four sessions of assessment were conducted. This period served as a baseline phase against which changes during treatment could be compared. Next, all patients participated in a two-week treatment program consisting of 10 daily sessions of exposure and response prevention. Finally, patients received an average of 10 additional sessions during a follow-up phase lasting three months to three years (mean of 15 months). Although self-report and assessor ratings did not change during the two-week baseline phase, the vast majority of patients improved during the two-week treatment phase. At follow-up, about two-thirds of patients were symptom-free, and all but three patients benefited to some extent from treatment.

Fals-Stewart, Marks, and Shafer (1993) studied behavioural therapy for 93 patients with DSM-III OCD, diagnosed by structured interviews. Patients were randomly assigned to: (1) 24 group sessions of behaviour therapy conducted in 12 weeks; (2) 24 individual sessions of behaviour therapy conducted in 12 weeks; and (3) 24 individual sessions of progressive muscle relaxation. Group and individual treatment led to significant improvement (e.g., 36% and 40% improvement in YBOCS scores, respectively) on all measures, whereas patients receiving progressive muscle relaxation did not improve significantly (e.g., 9% improvement in YBOCS scores). Although individual behaviour therapy was more effective than group behaviour therapy early in treatment, these two groups were equally effective by the end of treatment. Improvements were maintained at six-month follow-up.

CBT vs. Medication and Combined Treatment

Most controlled studies of CBT for OCD involve comparisons of CBT to pharmacological treatments and combined treatments. In an early study (Marks, Stern, Mawson, Cobb, and McDonald, 1980; Rachman et al., 1979) the efficacy of behaviour therapy (i.e., exposure plus response prevention) and clomipramine was studied. Forty patients were randomly assigned to treatment with clomipramine or placebo for eight months. From weeks four to seven, each group was randomly split into two groups receiving either exposure therapy or relaxation training. During weeks seven to 10, all groups received exposure therapy. Overall, clomipramine led to improvements in compulsive rituals, and in mood and social adjustment, but only in patients who were initially depressed. Exposure therapy led to significant improvements in rituals and in social adjustment, but to less change in mood. Relaxation produced little improvements. There was no interaction between clomipramine and exposure, although there appeared to be a slight additive effect.

Mawson, Marks, and Ramm (1982) published two-year follow-up data on 37 of the original 40 participants in this study. Although patients treated with exposure maintained gains achieved during exposure treatment, the effects of clomipramine on rituals were not maintained at two years.

Marks et al. (1988) examined the effects of clomipramine and exposure in a study of 49 patients with DSM-III diagnoses of OCD. This study included four groups, each of which received 27 weeks of medication treatment (clomipramine or placebo) and a behavioural intervention during weeks one through 23, as follows: (1) clomipramine plus anti-exposure instructions; (2) clomipramine plus self-exposure; (3) clomipramine plus self-exposure plus therapist-assisted exposure (weeks 8 to 23); and (4) placebo plus self-exposure plus therapist-assisted exposure. On most measures, self-exposure was significantly more effective than anti-exposure instructions. The effects of adding therapist-assisted exposure were minimal and lost by the end of week 23. Similarly, the effects of clomipramine were significant on a number of

measures, but these differences were not maintained by the end of treatment. The authors concluded that self-exposure instructions were the most potent component of treatment. At two-year follow-up, treatment gains were maintained and patients continued to be improved on all measures compared to pre-treatment. In addition, there continued to be no differences between groups (Kasvikis and Marks, 1988).

Because early uncontrolled studies tended to show that depression interferes with the effectiveness of behavioural treatments for OCD, Foa, Kozak, Steketee, and McCarthy (1992) tested the hypothesis that reducing depression with imipramine prior to behaviour therapy would enhance the effects of behaviour therapy for OCD. Patients meeting DSM-III criteria for OCD were divided into “highly depressed” and “mildly depressed” groups. Next, half of each group received imipramine whereas the remaining half received placebo for six weeks. All patients then received three weeks of intensive exposure and response prevention, followed by a course of supportive psychotherapy. Imipramine improved depression, but had no effect on OCD symptoms. In addition, neither level of depression or drug condition (i.e., imipramine vs. placebo) affected success in behaviour therapy. Approximately 45% of individuals were considered much improved following behavioural treatment, and an additional 53% were considered moderately improved. Supportive psychotherapy did not increase the percentage of individuals considered improved. Finally, 81% of individuals continued to be considered at least moderately improved at their last follow-up assessment (six, 12, or 24 months).

Finally, Cottraux et al. (1990) studied 60 patients with DSM-III diagnoses of OCD randomly assigned to 24 weeks of treatment in one of three groups: (1) fluvoxamine plus anti-exposure instructions; (2) fluvoxamine plus exposure; and (3) placebo plus exposure. OCD symptoms and depression improved in all three groups, with a tendency for combined treatment to be slightly more effective at 24 weeks, but not significantly so. Interestingly, participants in the anti-exposure group did not comply with instructions to avoid exposure to feared situations. Early in treatment, fluvoxamine had a greater impact on OCD symptomatology (but not depression); however this difference disappeared by post-treatment, at which point, the drug had a greater impact on depression but not on OCD rituals. By week 48, all group differences had

disappeared. Treatment gains were maintained, with no group differences at 18-month follow-up (Cottraux, Mollard, Bouvard, and Marks, 1993).

Predictors of CBT Outcome

Several studies have recently begun to examine predictors of therapeutic success during behavioural treatment of OCD. Basoglu, Lax, Kasvikis, and Marks (1988) found that poorer outcome was associated with more severe rituals, higher social desirability scores, being male, presence of checking rituals, bizarre and fixed rituals, and severe/unpredictable obsessions. Keijsers, Hoogduin, and Schaap (1994) found that greater initial severity of OCD and depression was associated with poorer outcome for compulsions. For obsessions, poorer outcome was associated with higher initial severity, initial depression, longer duration of illness, poorer motivation for treatment, and dissatisfaction with the therapeutic relationship. Finally, in a study by Buchanan, Meng, and Marks (1996), clinical improvement was associated with not having had previous treatment, being employed, having a fear of contamination, having overt behavioural rituals, low levels of depression, and living with one's family.

Summary

The psychological (CBT) treatment of choice appears to be exposure to feared situations combined with prevention of compulsive rituals. Relaxation training does not seem to be particularly helpful. Exposure and response prevention has been shown to be at least as effective as pharmacological approaches. Combinations of CBT and pharmacological treatments (imipramine and fluvoxamine) have also been shown to be effective.

Meta-Analytic Reviews

Several investigators have recently conducted meta-analyses of treatment outcome studies in OCD. Cox, Swinson, Morrison, and Lee (1993) analyzed studies of clomipramine, fluoxetine, and behaviour therapy and concluded that all were effective treatments for OCD, although not enough data were available to conclude that one treatment was superior to the others. A meta-analysis of antidepressants,

behaviour therapy and cognitive therapy by van Balkom et al. (1994) essentially confirmed the finding that all treatments are more effective than placebo but not different from one another, especially when comparisons were based on assessor ratings. However, when comparisons were based on patient ratings, behaviour therapy and combined treatment tended to be more effective than antidepressants.

A meta-analysis of drug treatments for OCD (Piccinelli, Pini, Bellantuono, and Wilkinson (1995) concluded that clomipramine and the selective serotonin reuptake inhibitors (SSRIs; e.g., fluvoxamine) were more effective than placebo or antidepressants without selective serotonergic properties. In addition, comparisons across drugs in the percent change in YBOCS scores suggest that clomipramine is more effective (61.3% improvement over placebo) than fluoxetine, fluvoxamine, and sertraline (28.5%, 28.2%, and 21.6% improvement over placebo, respectively). A meta-analysis by Stein, Spadaccini, and Hollander (1995) confirmed the superiority of clomipramine over other SSRI medications. One criticism of this conclusion is that many of the early studies of pharmacotherapy for OCD were conducted with clomipramine. Therefore, participants in these studies were more likely to have been treatment-naïve compared to participants in more recent studies with other medications, who are more likely to have tried multiple medications.

General Summary and Conclusions

Overall, there is evidence that OCD can be effectively treated by a variety of medications, especially serotonin specific agonists such as clomipramine, fluvoxamine, and fluoxetine. In addition, controlled studies of CBT consistently show that behavioural techniques are effective for OCD. In fact, the lack of physiological side effects and the tendency for treatment gains to be maintained after treatment is discontinued may make CBT the treatment of choice for many patients with OCD. Combinations of CBT and medications have also been shown to be effective in treating OCD.

Unfortunately, the majority of studies examining CBT for obsessions and compulsions were not discussed in this review because they failed to meet the criteria of including adequate controls and sample sizes. This is probably due in part to the relative lack of funding

available for behavioural studies. The majority of pharmacological studies reviewed were funded by pharmaceutical companies, and as such could afford more complicated designs and larger sample sizes.

Priorities for research in OCD should include continued research on psychosocial interventions for OCD, including exposure and response prevention, and cognitive therapy. More needs to be learned regarding the process of therapeutic change (i.e., how treatments work). In addition, many of the older uncontrolled studies should be repeated, using appropriate controls, adequate sample sizes,

diagnosis using DSM-IV criteria as measured by structured interviews, and adequate long-term follow-up, using a variety of outcome measures. Finally, although it is well established that drug treatments, psychological treatments, and their combinations are each effective for treating OCD, virtually nothing is known about how we might predict which treatment approach is likely to be more effective for particular patients.

Chapter 6

SOCIAL PHOBIA

Introduction

As with the other anxiety disorders, numerous uncontrolled studies have been conducted with patients who are socially anxious. Many studies were not based on specific diagnostic criteria, but rather included individuals who reported being shy, socially anxious or nervous in performance situations. Because social anxiety is common in individuals without any mental disorder and is often a feature of disorders other than social phobia, it is not clear how relevant the results of studies not based on DSM criteria are to individuals with social phobia. Therefore, as with other parts of this review, this section includes only controlled studies in which patients were properly diagnosed using DSM-III, DSM-III-R, or DSM-IV criteria.

A variety of treatments have been researched in people with social phobia. Among pharmacological approaches, benzodiazepines (e.g., clonazepam), monoamine oxidase inhibitors (MAOIs; e.g., phenelzine), reversible MAOI's (e.g., moclobemide), and SSRI antidepressants (e.g., sertraline) appear to be useful. In addition, psychological treatments such as exposure, cognitive therapy, and social skills training have been used effectively with individuals affected by social phobia. Currently, there are no published studies of self-help treatments for social phobia, although research on self-administered treatment is currently underway.

Medication Studies

Only six controlled studies meeting criteria for this review have been published. Munjack, Baltazar, Bohn, Cabe, and Appleton (1990) randomly assigned 23 patients with DSM-III-R diagnoses of social phobia (according to structured interviews) to eight weeks of treatment with clonazepam (mean

dose = 2.75 mg/day) or a non-treatment control condition. Compared to no treatment, clonazepam led to significant improvement on measures of social anxiety and avoidance, general anxiety, and global improvement. Initial sedation was the most common side effect, occurring in 70% of participants who took clonazepam.

Davidson et al. (1993) compared clonazepam (mean end-point dose = 2.4 mg/day) to placebo in a 10-week study with 75 patients who met DSM-III-R criteria (according to structured interviews) for social phobia. Clonazepam was superior to placebo on most measures (including measures of fear, avoidance, and global improvement). Response rates were 78.3% for clonazepam and 20.0% for placebo, based on clinician's ratings of global improvement. Clonazepam seemed to improve performance-based and generalized social phobia.

In a study comparing phenelzine (mean dose = 75.7 mg/day) atenolol, (mean dose = 97.6 mg/day), and placebo, Liebowitz et al. (1988, 1992) treated 74 patients meeting DSM-III-R criteria for social phobia in an eight-week, double-blind trial. Response rates were 64% for phenelzine, 30% for atenolol, and 23% for placebo. On a variety of measures, phenelzine was superior to atenolol and placebo. Atenolol and placebo did not differ significantly on any measures. After eight weeks, responders continued to take their medications for an additional eight-week maintenance phase. By the end of week 16, phenelzine was still significantly superior to placebo; however, atenolol response was intermediate and did not differ significantly from either phenelzine or placebo. Response to phenelzine was particularly strong in patients with generalized social phobia (76% of sample). Although not reported in this study, side effects have been identified with use of phenelzine and other irreversible MAO inhibitors. These include possible hypertensive crises when combined with certain foods and medications, and possible toxicity to the liver. These side effects are not evident in the newer reversible MAO inhibitors (Canadian Mental Health Association, 1995).

Versiani et al. (1992) compared eight weeks of treatment with phenelzine (mean dose = 67.5 mg/day), moclobemide (mean dose = 580.7 mg/day), and placebo in 78 patients with a DSM-III-R diagnosis of social phobia (assessed by structured interviews). By week 8, both active drugs led to significantly more improvement than placebo, with phenelzine being more effective than moclobemide on several measures. During the maintenance phase (weeks eight to 16), patients (especially those taking moclobemide) continued to improve to some extent, so that by week 16, 91% of patients taking phenelzine and 82% of those taking moclobemide were almost asymptomatic. Moclobemide was associated with fewer and less severe side effects than phenelzine, especially in weeks eight to 16. Common side effects of moclobemide included dizziness, fatigue, insomnia, dry mouth and headache. Phenelzine was associated with fatigue, orthostatic hypotension, insomnia, dry mouth, dizziness, constipation, decreased or loss of libido, and retarded/inhibited ejaculation.

Sertraline (mean dose = 133.5 mg/day) was compared to placebo in a double-blind crossover study with 12 patients who met DSM-III-R criteria for social phobia (Katzelnick et al., 1995). All patients received 10 weeks of each treatment in random order. Sertraline, but not placebo, led to a significant improvement in social phobia symptoms.

Finally, brofaromine (fixed dosage = 150 mg/day) was compared to placebo in a 12-week trial with 77 patients who met DSM-III-R criteria for social phobia (according to structured interviews). Seventy-eight percent of those taking brofaromine and 23% of those taking placebo were judged to be "much improved" or "very much improved" on the Clinical Global Impression Scale. In addition, brofaromine led to more improvement than placebo on a variety of measures of social anxiety and depression, although after treatment, patients on active medication still scored higher than normal controls on a measure of social anxiety. During the nine-month maintenance treatment phase, patients taking brofaromine continued to improve, whereas 60% of placebo responders relapsed during this period.

Summary and Conclusions

Clonazepam, phenelzine, moclobemide, sertraline, and brofaromine each appear to be effective for treating social phobia. Phenelzine and other irreversible MAO inhibitors are associated with side effects including possible hypertensive crises when combined with certain foods and medications, and possible toxicity to the liver. Beta blockers (e.g., atenolol) are not significantly more effective than placebo. More studies are needed to replicate research demonstrating the efficacy of these medications as well as additional drugs that have not yet been studied in controlled trials.

Studies of CBT

CBT vs. Supportive Therapy or Wait-List

In a study of 49 individuals who met DSM-III criteria for social phobia (according to structured interviews), Heimberg et al. (1994) compared twelve sessions of group CBT (including exposure and cognitive strategies) to a control condition in which groups received education and support. Outcome was assessed using clinician ratings, as well as self-report, behavioural, physiological, and cognitive assessments. Both groups were improved on most measures; however, those in the CBT group were rated as more improved and reported less anxiety during a behavioural test, relative to controls. At six-month follow-up, gains were maintained, and patients who had received CBT continued to be more improved than those in the control condition on a few measures. Nineteen participants were available for follow-up 4.5 to 6.4 years later (Heimberg, Salzman, Holt, and Blendell, 1993). At long-term follow-up, patients who had received CBT were significantly more improved than those in the control condition on most measures.

Newman, Hofmann, Trabert, Roth, and Taylor (1994) investigated the effectiveness of exposure therapy (without cognitive interventions) for 36 individuals with social phobia (DSM-III-R criteria, based on structured interviews) who specifically reported heightened fear when speaking in public. Participants were randomly assigned to eight weekly sessions of exposure therapy or a wait-list control group. Relative to the wait-list control group, exposure led to significant changes on measures of behavioural, subjective, and cognitive anxiety.

CBT vs. Pharmacological Treatments

Turner, Beidel, and Jacob (1994) compared three months of behaviour therapy (flooding), atenolol (fixed final dosage = 100 mg/day), and placebo in 72 patients who met DSM-III-R criteria for social phobia (based on structured interviews). Flooding was consistently better than placebo, whereas atenolol was not. Flooding was superior to atenolol on several measures. The percentages of patients who improved at least moderately were 88.9% for exposure, 46.6% for atenolol, and 43.8% for placebo. Regardless of treatment condition, patients continued to differ from normal comparison subjects at post-treatment. At six-month follow-up, participants who had improved maintained their gains.

Gelernter et al. (1991) randomly assigned 65 patients with social phobia (DSM-III criteria, according to structured interviews) to four 12-week treatment conditions: (1) CBT; (2) phenelzine (mean dose = 55 mg/day) plus self-exposure instructions; (3) alprazolam (mean dose = 4.2 mg/day) plus self-exposure instructions; and (4) placebo plus self-exposure instructions. All groups improved significantly across measures from pre- to post-treatment. Overall, the four treatments did not significantly differ from one another on most measures. Based on changes on the social phobia subscale of the Fear Questionnaire, the percentages of patients who were considered to be responders (i.e., scoring below the mean of the general population) were 63% for phenelzine, 38% for alprazolam, 24% for CBT, and 20% for placebo.

Finally, Heimberg et al. (1994) reported the results of an unpublished study comparing 12 weeks of CBT, phenelzine, placebo, and supportive psychotherapy. Participants included 133 individuals meeting DSM-III-R criteria for social phobia (according to structured interviews). CBT and phenelzine were equivalent after 12 weeks and superior to placebo and supportive psychotherapy. Almost 80% of individuals in the CBT and phenelzine groups were considered to be responders, compared to less than 40% of the other two groups. Phenelzine worked more quickly than CBT, and was somewhat more effective than CBT on several measures at post-treatment. Improvement among

patients in the CBT and phenelzine groups was maintained following a six-month maintenance period. However, upon discontinuation following the six-month follow-up, half of patients on phenelzine relapsed, whereas those who had CBT maintained their gains.

Studies Comparing Different CBT Strategies

Numerous studies have examined the relative and combined effects of various cognitive and behavioural strategies. In an early study, Butler, Cullington, Munby, Amies, and Gelder (1984) randomly assigned patients to seven weekly sessions of: (1) exposure; (2) exposure plus anxiety management (i.e., relaxation, distraction, rational self-talk); or (3) a wait-list control condition. Participants were 45 patients with a DSM-III diagnosis of social phobia. At post-treatment and six-month follow-up, both treatments led to significantly more improvement than the wait-list condition. Exposure plus anxiety management was superior to exposure alone on two out of six measures at post-treatment and on all six measures at follow-up. In addition, whereas no patients in the combined treatment sought additional treatment during the follow-up, 40% of those in the exposure only group sought additional help.

Emmelkamp, Mersch, Vissia, and van der Helm (1985) treated 34 individuals with a DSM-III diagnosis of social phobia using six sessions of: (1) exposure in vivo; (2) rational-emotive therapy (i.e., cognitive therapy); or (3) self-instructional training (i.e., imaginal exposure). All three groups improved on phobic and social anxiety measures and there were few significant differences among groups. For all three groups, these improvements were either maintained or enhanced at one-month follow-up.

Mattick and Peters (1988) treated 41 individuals who met DSM-III criteria for social phobia in six weekly sessions of: (1) guided exposure; or (2) guided exposure plus cognitive restructuring. Overall, participants improved from pre- to post-treatment on all outcome measures, and combined treatment led to significantly more improvement than exposure alone on two measures of social avoidance. Percentages of patients considered to have achieved a high or very high rate of improvement were 95% for combined treatment and 56% for exposure only.

In a related study, Mattick, Peters, and Clarke (1989) treated 43 patients with DSM-III diagnoses of social phobia in six weekly sessions of: (1) exposure only; (2) cognitive restructuring only; (3) exposure plus cognitive restructuring; or (4) a wait-list control condition. Patients who received cognitive restructuring or combined treatment improved on all measures, whereas those who received exposure only tended to improve on avoidance measures but not attitudinal measures. The percentages of patients meeting composite criteria for high or very high rates of improvement were 27% for exposure only, 45% for cognitive restructuring only, and 72% for combined treatment. Between-group analyses at post-treatment showed that combined treatment was superior to exposure on two phobia measures, whereas combined treatment and exposure were superior to cognitive restructuring on the behavioural approach test used in the study. The behavioural test represented the range of activities avoided by study participants.

Mersch, Emmelkamp, Bögels, and van der Sleen (1989) treated 39 patients who met DSM-III-R criteria for social phobia. Based on extreme scores on a behavioural test and on cognitive measures, participants were classified as primarily cognitive reactors or behavioural reactors. Half of each group received an eight-week behavioural treatment (social skills training) and the other half received a cognitive treatment (rational-emotive therapy) lasting eight weeks. All treatment groups improved and there was no support for the hypothesis that matching treatment type with patient response style would lead to greater improvement. Overall, results were maintained at 14-month follow-up (Mersch, Emmelkamp, and Lips, 1991).

Scholing and Emmelkamp (1993a) randomly assigned 73 patients who met DSM-III-R criteria for generalized social phobia (diagnosed by structured interviews) to 16 sessions of group or individual treatment with one of three treatment packages: (1) two blocks of exposure therapy; (2) one block of cognitive therapy followed by one block of exposure; or (3) two blocks of CBT in which exposure and cognitive therapy were integrated from the beginning. Each block of treatment lasted four weeks and blocks were separated by a four-week block without any treatment. Overall, each treatment

was effective. Following the first treatment block, there were no differences among treatments, except that the integrated treatment was less effective than the other two treatments for decreasing somatic complaints. At three-month follow-up, cognitive group treatment was the most effective, and integrated group treatment was the least effective. Using an identical design with the same inclusion criteria and the same three treatment groups (although all participants were treated individually), Scholing and Emmelkamp (1993b) treated 30 patients with social phobia who specifically reported concerns about blushing, sweating, or trembling. All three treatments led to significant improvements and there were no significant differences between treatments. Gains were maintained at follow-up.

In a study by Mersch (1995), 34 patients with DSM-III-R diagnoses of social phobia were randomly assigned to 14 weekly sessions of: (1) exposure therapy; (2) integrated CBT (including exposure, rational-emotive therapy, and social skills training); or (3) a wait-list control condition. Both treatments led to significantly more improvement than the wait-list control condition on almost all measures. However, the two treatments did not significantly differ from one another on any measures. Treatment gains were maintained over three- and 18-month follow-up periods, with neither group proving to be superior.

Finally, Hope, Heimberg, and Bruch (1995) randomly assigned 43 individuals with DSM-III-R diagnoses of social phobia (based on structured interviews) to 12 weekly group sessions of: (1) CBT (including exposure and cognitive restructuring); (2) exposure only; or (3) a wait-list comparison condition. In general, participants in the treatment conditions improved on a variety of measures, whereas those on the wait-list tended not to improve. Whereas CBT tended to lead to greater improvements on some measures (e.g., anxiety during a behavioural test), exposure led to more gains on other measures. The percentages of patients classified as responders (i.e., social anxiety no longer clinically significant) were 36.4% for CBT, 70% for exposure, and 0% for wait-list. Gains were maintained at six-month follow-up, although there were fewer measures on which the treatment groups differed.

Summary

There appears to be much evidence to suggest that CBT is an effective treatment for social phobia. CBT appears to be more effective than supportive psychotherapy, placebo, and no treatment at all. In addition, preliminary research suggests that CBT is at least as effective as pharmacological approaches in the short-term and probably more effective than medications in the long-term.

Meta-Analytic Reviews

In several studies, the combination of cognitive and behavioural techniques has appeared to be more helpful than exposure-based strategies alone. However, a recent meta-analysis comparing cognitive-behavioral packages and pure exposure-based treatments for social phobia (Feske and Chambless, 1995) found no differences overall. In other words, adding cognitive strategies to exposure-based therapies did not seem to affect the outcome. Length of treatment was also unrelated to outcome, although a larger number of exposure sessions was associated with better results.

General Summary and Conclusions

Although few controlled pharmacological trials exist for social phobia, preliminary evidence suggests that a variety of drugs may be effective, including clonazepam, phenelzine, sertraline, and brofaromine. Additional medication studies are clearly needed to establish the effectiveness of anti-anxiety drugs and antidepressants for social phobia. Preliminary studies suggest that beta blockers such as atenolol are not especially useful for generalized social phobia. Nevertheless, they are commonly used in clinical practice to treat discrete social phobias (e.g., public speaking phobias). Despite evidence that beta blockers help to reduce anxiety in normal stage fright among musicians, actors, and other

performers, their usefulness among individuals who meet full criteria for discrete social phobias has yet to be established.

There appears to be much evidence to suggest that CBT is an effective treatment for social phobia. CBT appears to be more effective than supportive psychotherapy, placebo, and no treatment at all. In addition, preliminary research suggests that CBT is at least as effective as pharmacological approaches in the short-term and probably more effective than medications in the long-term. Much more research is required before such a conclusion can be drawn with confidence. In addition, there are no published studies examining the efficacy of combined psychological and pharmacological treatments for social phobia.

Studies comparing various methods used in CBT have yielded conflicting results. Some studies have found no differences between the effectiveness of cognitive strategies, behavioural strategies, and their combination; others have found advantages of one treatment over the other. In several studies, the combination of cognitive and behavioural techniques has appeared to be more helpful than exposure-based strategies alone. However, a recent meta-analysis comparing cognitive-behavioral packages and pure exposure-based treatments for social phobia (Feske and Chambless, 1995) found no differences overall. In other words, adding cognitive strategies to exposure-based therapies did not seem to affect the outcome. Length of treatment was also unrelated to outcome, although a larger number of exposure sessions was associated with better results.

In summary, many questions remain to be answered regarding the treatment of social phobia. Of particular importance is establishing the comparative efficacy of medications, psychological treatments, and combined treatments that are currently used in clinical practice. In addition, future research should consider predictors of outcome with different treatment approaches. Finally, the role of self-help approaches in social phobia remains to be studied.

Chapter 7

GENERALIZED ANXIETY DISORDER

Introduction

Of all the anxiety disorders, the diagnostic criteria for generalized anxiety disorder (GAD) have undergone the most extensive revisions since the disorder was first introduced in DSM-III (American Psychiatric Association, 1987). At that time, the earlier diagnosis of “anxiety neurosis” was split into two disorders: panic disorder and GAD. GAD was conceptualized as a residual category for individuals with heightened anxiety lasting at least one month, and who were not phobic, did not meet criteria for panic disorder, and who were not depressed.

With the publication of DSM-III-R (American Psychiatric Association, 1987), GAD was defined as a disorder in which the hallmark was excessive or unrealistic worry about two or more life spheres (e.g., work, family), lasting at least six months, and accompanied by six of 18 associated symptoms. In DSM-IV (American Psychiatric Association, 1994), GAD is still a disorder of excessive worry lasting six months or more; however, the criteria have been revised, so that the worry must be difficult to control, be focused on a variety of topics (rather than two or more life spheres), and be associated with three out of six symptoms. As a result of the changes to the GAD diagnostic criteria, it is likely that many of the participants from early studies (before DSM-III-R) would not meet criteria for GAD by DSM-IV standards. Because of a relative lack of recent studies, this review will include studies with patients meeting GAD based on DSM-III or more recent criteria (diagnostic criteria will be specified for each study reviewed).

Medications that appear to be effective for GAD include benzodiazepines (e.g., diazepam, lorazepam, alprazolam), buspirone, and antidepressants (e.g., imipramine). In addition, cognitive-behavioural

strategies such as cognitive restructuring and relaxation-based treatments seem to be as effective as medications for treating GAD.

Medication Studies

Studies Involving Buspirone

Buspirone vs. Diazepam

Six studies were found in which buspirone, diazepam and placebo were compared for individuals with GAD. Rickels et al. (1982) studied 240 individuals meeting DSM-III criteria for GAD. Patients were randomly assigned to four weeks of treatment with buspirone (15 - 20 mg/day), diazepam (15 - 20 mg/day), or placebo. Although both drugs were more effective than placebo on measures of generalized anxiety, diazepam seemed to have a greater effect on somatic symptoms, whereas buspirone led to greater improvement on symptoms associated with cognitive and interpersonal problems. Pecknold et al. (1989) replicated these results, showing that buspirone and diazepam were equally effective to one another and more effective than placebo.

Ross and Matas (1987) treated 30 individuals (i.e., treatment completers) meeting DSM-III criteria for GAD with four weeks of buspirone (maximum dose = 40 mg/day), diazepam (maximum dose = 40 mg/day), or placebo. There were no group differences on any scales, which included measures of global functioning, generalized anxiety, and general psychopathology.

Olajide and Lader (1987) conducted a crossover study with 33 patients meeting DSM-III criteria for GAD. Participants were treated over nine weeks (in three-week phases) with diazepam (mean dosage = 20 mg/day), buspirone (mean dosage = 20 mg/day),

and placebo using a Latin-square design. Drug phases were not separated by washout periods. On most measures, diazepam was superior to buspirone and placebo. Buspirone and placebo did not significantly differ on outcome measures. In addition, although there was only one dropout during the placebo and diazepam conditions, six patients in the buspirone condition discontinued treatment. This study is limited by the possibility of carry-over effects across medications, since, as mentioned, drugs were not discontinued for any length of time between phases. In addition, most patients had been on benzodiazepines before beginning the study and were unable to discontinue their previous medications during the initial pre-treatment washout. In other words, buspirone may have been introduced when patients were experiencing benzodiazepine withdrawal symptoms.

Two studies were found in which buspirone and diazepam were compared without a placebo condition. Participants in both studies were diagnosed according to DSM-III criteria. In the first study, Jacobson, Dominguez, Goldstein, and Steinbook (1985) treated 66 individuals (39 completers) with four weeks of buspirone (mean final dosage = 25.5 mg/day) or diazepam (mean final dosage = 15 mg/day). Diazepam showed earlier effects than buspirone, although both drugs were equivalent by the end of treatment. Diazepam was associated with more severe side effects than buspirone. Finally, Murphy, Owen, and Tyrer (1989) studied 51 patients taking 7.5 to 11.5 mg/day of diazepam or buspirone for either six weeks or 12 weeks, after which medications were abruptly discontinued and patients were maintained on placebo until week 14. Seventy-three percent of the 11 dropouts were in the buspirone treatment group. Both drugs led to decreased anxiety, although diazepam worked more quickly, had more side effects, and was associated with more severe symptoms upon discontinuation.

Other Buspirone Studies

In a four-week study of 335 patients with DSM-III diagnoses of GAD, Sacchetti, Zerbini, Banfi, and Tansella (1994) compared buspirone (mean dosage = 15.2 - 15.5 mg/day) to lorazepam (mean dosage = 3.5 mg/day), diazepam (mean dosage = 15.45 mg/day), or bromazepam (mean dosage = 9.03 mg/day). With the exception of some minor differences, buspirone did not differ from any of the other drugs in terms of dropout rate, improvement on measures of anxiety and global functioning, side effects, and timing of clinical response. On measures of anxiety and global improvement, participants in each group appeared to improve.

Rickels, Schweizer, Csanalosi, Case, and Chung (1988) studied the effects of abrupt discontinuation of clorazepate (mean dosage = 33 mg/day) and buspirone (mean dosage = 27 mg/day) following six months of treatment in a study with 65 patients, of whom 87% had DSM-III diagnoses of GAD and 13% met criteria for panic disorder. Although both medications were equally effective during treatment, the buspirone group had a higher dropout rate than the clorazepate group during the acute treatment phase (45% vs. 26%). The authors suggested that a slower improvement rate for buspirone relative to clorazepate was an important variable contributing to the dropout rate. They also suggested that the dropout rate reflected lower patient satisfaction with buspirone (than with clorazepate). Nonetheless, upon discontinuation, patients taking clorazepate experienced significant withdrawal symptoms, whereas those taking buspirone did not.

Cohn and Wilcox (1986) compared buspirone (maximum dosage = 50 mg/day), alprazolam (maximum dosage = 5 mg/day), and lorazepam (maximum dosage = 10 mg/day) in a four-week study of 60 patients meeting DSM-III criteria for GAD. All three medications led to improvement and were equally effective on measures of anxiety and global improvement. Side effects were less frequent with buspirone than with either lorazepam or alprazolam.

Finally, Enkelmann (1991) compared alprazolam (mean final dosage = 1.9 mg/day), buspirone (mean daily dosage = 18.7 mg/day), and placebo in a six-week study of 94 patients meeting DSM-III criteria for GAD. On measures of global functioning, anxiety, and depression, alprazolam and buspirone were equally effective and more effective than placebo, although alprazolam led to more rapid improvement than did buspirone. Although side effects were equally severe in the two groups, buspirone tended to be associated with gastrointestinal system side effects (e.g., abdominal discomfort, disturbed appetite), whereas alprazolam was more often associated with symptoms such as drowsiness and sedation. As with previous studies, buspirone was associated with a higher dropout rate than alprazolam. Similar to Rickels et al. (1988)(above), Enkelmann attributed the higher dropout rate to the length of time needed for buspirone to achieve maximal therapeutic effect (five to six weeks), relative to the time needed for alprazolam to achieve its therapeutic effect (within the first week of treatment).

Studies Involving Alprazolam

In addition to the comparisons with buspirone reviewed earlier, alprazolam has been compared to a variety of other medications for GAD. In a six-week double-blind study, Hoehn-Saric, McLeod, and Zimmerli (1988) examined the effects of six weeks of alprazolam (mean final dosage = 2.2 mg/day) and imipramine (mean final dosage = 91 mg/day) for 60 patients with DSM-III diagnoses of GAD (with duration of at least six months). Overall, both drugs led to improvement on most measures and there were few differences between drug conditions. However, on some measures, alprazolam seemed to lead to a greater reduction in somatic symptoms, whereas imipramine led to more improvement on psychic symptoms (e.g., negative thinking, and dysphoria).

Elie and Lamontagne (1984) compared alprazolam (optimal dosage = 2 mg/day) and diazepam (optimal dosage = 15.8 mg/day) in a four-week study with 48 patients meeting DSM-III criteria for GAD. Based

on measures of anxiety, global functioning, and depression, both groups improved significantly from baseline and there were few significant differences between groups. Castillo, Sotillo, and Mariategui (1987) compared eight weeks of alprazolam (mean dosage = 2.04 mg/day), clobazam (mean dosage = 43.60 mg/day), and placebo for 96 patients meeting DSM-III criteria for GAD. Although the active treatment groups improved more quickly than participants taking placebo, all three groups showed significant improvement by the end of treatment and there were few significant group differences.

Finally, Frattola et al. (1994) compared alprazolam (fixed dosage = 1.5 mg/day) and alpidem (fixed dosage = 150 mg/day) in 122 patients meeting DSM-III-R criteria for GAD. Following six weeks of active treatment, patients were withdrawn from medication during a two-week placebo-withdrawal phase. Both medications led to significant improvement on measures of anxiety and there were no significant differences. During the withdrawal phase, patients taking alprazolam returned to baseline levels of anxiety, whereas those patients taking alpidem experienced only a slight increase in anxiety, but still showed significant improvement overall.

Studies Involving Bromazepam

Kragh-Sorensen et al. (1990) compared bromazepam (fixed dosage = 6 mg/day), chlorprothixene (fixed dosage = 30 mg/day), and placebo in a two-week study with 245 patients meeting DSM-III criteria for GAD. Anxiety improved significantly in all three groups following treatment. Bromazepam led to significantly more improvement than placebo, but was not significantly better than chlorprothixene. Percentages of patients in each group reporting at least moderate improvement were 79.3% for bromazepam, 71.7% for chlorprothixene, and 64.5% for placebo. Fontaine, Mercier, Beaudry, Annable, and Chouinard (1986) conducted a similar study comparing four weeks of treatment with bromazepam (12 or 18 mg/day), lorazepam (4 or 6 mg/day), or placebo. Participants were 60 patients meeting GAD criteria according to an early draft of DSM-III published in 1978 (similar to DSM-III criteria, except for a minimum duration of six months and an onset not associated with a psychosocial stressor). Both drugs were significantly more effective than placebo on a variety of measures, although there were no differences between the anxiolytic effects of the two active treatments.

Finally, Fontaine, Chouinard, and Annable (1984) examined the effects of abrupt or gradual discontinuation (over a period of three weeks) following four weeks of treatment of bromazepam (18 mg/day), diazepam (15 mg/day), or placebo. Participants were 48 individuals who met criteria for GAD according to the 1978 draft of DSM-III (see above description). During the acute treatment phase, patients treated with active medication showed more improvement than those on placebo, and bromazepam tended to be more effective than diazepam. Following drug discontinuation, patients who were withdrawn abruptly from active medication showed significantly worse symptoms compared to those who were withdrawn from placebo. However, there were no differences between individuals withdrawn gradually from medication and those withdrawn from placebo. Withdrawal symptoms for bromazepam and diazepam were not significantly different, although there was a non-significant tendency for bromazepam to be associated with more withdrawal symptoms.

Other Benzodiazepine Studies

Rickels, Downing, Schweizer, and Hassman (1993) compared diazepam (mean maximum dosage = 26 mg/day), imipramine (mean maximum dosage = 143 mg/day), trazodone (mean maximum dosage = 255 mg/day), and placebo in an eight-week study of 230 patients with DSM-III diagnoses of GAD, and with no major depression or panic disorder. Although patients taking diazepam responded earlier to treatment, by week eight, trazodone was as effective as diazepam and imipramine was more effective than diazepam on measures of psychic anxiety (e.g., tension, apprehension, worry). The percentages of completers judged to be moderately to markedly improved were 73% for imipramine, 69% for trazodone, 66% for diazepam, and 47% for placebo.

Cutler, Sramek, Wardle, Hesselink, and Roeschen (1993) compared lorazepam (maximum dose 2-6 mg/day), ipsapirone (a derivative of buspirone; maximum dose 11-30 mg/day), and placebo in a four-week study (with an additional four-week

extension) with 90 patients meeting DSM-III criteria for GAD. Both drugs were significantly more effective than placebo at four and eight weeks, with no differences between them. Patients experienced a 50% reduction in anxiety on active medication and a 20% reduction on placebo. Following a two-week placebo washout, anxiety rebounded in patients taking lorazepam, but not in those taking ipsapirone.

Casacchia, Bolino, and Ecarl (1990) treated 36 patients with DSM-III-R diagnoses of GAD using 1 mg/day of etizolam, .5 mg/day of etizolam, or placebo for five weeks. At the higher dosage, etizolam led to greater improvement for anxiety and depression (particularly somatic symptoms) than the lower dosage of either etizolam or placebo. Few side effects were reported.

Other Medication Studies

Trifluoperazine (2 to 6 mg/day) was compared to placebo in a four-week study of 415 patients meeting DSM-III criteria for GAD (Mendels et al., 1986). On a variety of anxiety measures, trifluoperazine led to more improvement than did placebo. Those taking medication did not report significantly more side effects than those taking placebo.

Adams et al. (1995) compared 300 mg/day of CI-988 (a CCK_B antagonist) to placebo in a four-week study of 88 patients with a DSM-III-R diagnosis of GAD. Changes in anxiety (based on a variety of measures) were not significantly different between the two groups.

Finally, CGP361A (a new beta blocker; 2 mg/day), flupenthixol (a neuroleptic; 2 mg/day), and placebo were compared in a four-week study of 61 patients with DSM-III diagnoses of GAD (Bjerrum, Allerup, Thunedborg, Jakobsen, and Bech, 1992). The percentages of patients who were judged to be responders (50% or more reduction on a particular measure) were not significantly different across groups for any measures. The percentage of patients considered responders on various measures of anxiety and global improvement ranged from 33.3% to 78.9% for CGP361A, 30.7% to 80% for flupenthixol, and 36.4% to 56.3% for placebo.

Summary

A variety of medications have been shown to be helpful for individuals suffering from GAD. Benzodiazepines (e.g., diazepam, lorazepam, alprazolam) tend to work more quickly than other medications that have been shown to be useful (e.g., buspirone), although they may be associated with more severe side effects with a rebound effect when medication is discontinued. Antidepressants, such as imipramine seem to be helpful for GAD, although more research is needed using newer SSRI antidepressants such as sertraline and paroxetine. In addition, more studies are needed using recent diagnostic criteria.

Studies of CBT

CBT vs. Alternative Treatments

Durham et al. (1994) randomly assigned 110 patients with DSM-III-R diagnoses of GAD (diagnosed by structured interviews) to six months of treatment in five conditions: (1) anxiety management training (six to eight sessions of education and new coping strategies); (2) cognitive therapy (six to eight sessions); (3) cognitive therapy (16-20 sessions); (4) analytic psychotherapy (six to eight sessions); and (5) analytic psychotherapy (16-20 sessions). On four out of nine measures of anxiety, depression, and global functioning, cognitive therapy led to more improvement than analytic psychotherapy. Anxiety management led to improvements that were similar to cognitive therapy. The percentages of patients judged to be at least moderately improved were 76% with cognitive therapy, 49% with anxiety management, and 42% with analytic psychotherapy. At six-month follow-up, two-thirds of patients receiving cognitive therapy had returned to normal functioning on the two measures examined, whereas one-third or fewer patients in the other groups were functioning normally. Duration of treatment (i.e., six to eight sessions compared to 16-20 sessions) was not related to outcome.

CBT vs. Pharmacological Treatments

In the only study to examine the relative and combined effects of CBT and medication for GAD, Power, Simpson, Swanson, and Wallace (1990a, 1990b) treated 101 patients meeting DSM-III criteria for GAD in five conditions: (1) diazepam; (2) placebo; (3) CBT; (4) CBT plus diazepam; and (5) CBT plus placebo. Participants receiving either diazepam (fixed dose of 15 mg/day) or placebo took the medication for six weeks, followed by a three-week, placebo-controlled discontinuation. Those in the CBT groups received up to seven sessions of CBT over nine weeks. Immediately following treatment and at six-month follow-up, groups receiving CBT (especially CBT alone and CBT plus diazepam) improved the most. Overall, diazepam was no more effective than placebo, possibly due to the low fixed dose schedule. The percentages of patients achieving clinically significant change on the Hamilton Anxiety Rating Scale were 90.5% (CBT plus diazepam), 85.7% (CBT), 83.3% (CBT plus placebo), 68.2% (diazepam), and 36.8% (placebo). Groups taking diazepam did not experience significant return of anxiety symptoms during the graded withdrawal phase.

Studies Comparing Different CBT Strategies

Blowers, Cobb, and Mathews (1987) treated 66 patients meeting DSM-III criteria for GAD with eight sessions (10 weeks) of: (1) CBT (relaxation plus cognitive therapy); (2) non-directive psychotherapy; and (3) wait-list control condition. CBT was significantly more effective than wait-list on almost all measures, but only differed from non-directive psychotherapy on a few measures at post-treatment and at six-month follow-up.

Borkovec et al. (1987) treated 30 individuals with DSM-III diagnoses of GAD (according to structured interviews) using 12 sessions of relaxation training plus cognitive therapy or relaxation training plus non-directive therapy. Overall, patients in both groups improved from pre- to post-treatment on all measures (including self-report questionnaires, assessor-rated scales, and daily diaries). Cognitive therapy led to greater improvements than did non-directive therapy on several self-report measures, although these differences were no longer present in the 16 individuals available at follow-up, six to twelve months later.

In a follow-up study using DSM-III-R criteria (based on structured interviews), Borkovec and Costello (1993) treated 55 individuals with GAD in three treatment conditions: (1) applied relaxation; (2) CBT; and (3) non-directive psychotherapy. Overall, CBT and relaxation were equivalent to one another and superior to non-directive psychotherapy. Gains were maintained at follow-up (six and twelve months) for the CBT and relaxation groups, whereas those receiving non-directive psychotherapy experienced a worsening of symptoms during follow-up. The percentages of patients meeting criteria for high responder status at post-treatment were 72.2% (relaxation), 57.9% (CBT), and 22.2% (non-directive psychotherapy). At 12-month follow-up, these percentages were 66.7%, 84.2%, and 38.9%, respectively. Furthermore, for patients who responded to treatment, there was a substantial decrease in the prevalence of comorbid diagnoses (the majority of which were social phobia and simple phobia) as well (Borkovec, Abel, and Newman, 1995).

Barlow, Rapee, and Brown (1992) randomly assigned 65 patients with DSM-III-R diagnoses of GAD (diagnosed with structured interviews) to 15 weeks in one of four conditions: (1) relaxation; (2) cognitive therapy; (3) relaxation plus cognitive therapy; or (4) wait-list control. On several measures, including measures of worry, patients in the treated groups did significantly better than those on the wait-list and no significant differences were found among active treatments. The percentages of patients judged to be treatment responders at post-treatment were 0% (wait list), 36% (relaxation plus cognitive therapy), 63% (relaxation), and 67% (cognitive therapy). Overall, gains shown at post-treatment were maintained throughout the two-year follow-up period.

Butler, Fennell, Robson, and Gelder (1991) randomly assigned 57 patients meeting DSM-III-R criteria for GAD (based on structured interviews) to four to 12 sessions of: (1) behaviour therapy (i.e., progressive muscular relaxation, exposure, self-

reward); (2) cognitive-behavioural therapy; or (3) wait-list control. At post-treatment, improvement following cognitive-behavioural therapy was significantly greater than improvement for wait-list patients on 13 of 16 measures (including measures of anxiety, depression, and cognition). Behaviour therapy was superior to wait-list on four of 16 measures. Cognitive-behavioural therapy was superior to behaviour therapy on six of 16 measures. These results were maintained at six-month follow-up.

Finally, White, Keenan, and Brooks (1992) treated 109 patients with DSM-III-R diagnoses of GAD (based on structured interviews) with six sessions of: (1) cognitive therapy; (2) behaviour therapy; (3) cognitive and behaviour therapy; (4) placebo treatment (involving listening to audio tapes supposedly containing subliminal messages); and (5) wait-list. A variety of measures for anxiety, depression, and global ratings were included. At post-treatment, all conditions showed significant improvements on most measures, with the active treatments (and to some extent, the placebo condition) being more effective than wait-list. On most measures, there were no significant differences between the four treatment groups, although the placebo condition tended to lead to less change (although not significantly so) than did the active treatment conditions. Those in the cognitive and behavioural treatment conditions continued to improve during the six-month follow-up phase, whereas those in the placebo condition maintained their gains without further improvement.

Summary

A variety of approaches appear to be helpful for patients with GAD, including cognitive strategies (e.g., cognitive restructuring) and behavioural strategies (e.g., relaxation training). Although some studies have shown differences in the effectiveness of different cognitive and behavioural treatments, most studies have found few differences in the effectiveness of these approaches.

General Summary and Conclusions

Overall, there appears to be effective pharmacological and psychological treatments for generalized anxiety disorder. Among medication studies, all but two of the studies reviewed were based on patients diagnosed according to DSM-III criteria. As mentioned earlier, the criteria for GAD underwent extensive revisions when DSM-III-R was published, so it is difficult to know how relevant the findings from earlier studies are to patients diagnosed by current DSM criteria. In addition, the majority of pharmacological studies of GAD patients used few measures, relative to studies of psychological treatments. In any case, to the extent that early pharmacological studies are relevant to individuals diagnosed according to DSM-III-R and DSM-IV, a variety of medications appear to be helpful, including buspirone, imipramine, and a range of benzodiazepines. With a few exceptions, most studies have found these medications to be more effective than placebo. Few differences have been reported among medications. One exception is the finding in several studies that benzodiazepines work more quickly than other medications (but are associated with withdrawal symptoms and a rebound effect).

In general, CBT studies were more likely than medications to have used structured interviews to diagnose patients according to DSM-III-R criteria. In addition, a broader range of outcome measures have been used in CBT studies, including instruments designed to measure worry. In the two studies in which CBT was compared to alternative treatments, CBT was found to be more effective than analytic psychotherapy or diazepam, although more

studies are needed before any firm conclusions can be drawn regarding the relative efficacy of CBT and other approaches. In addition, CBT appears to be more effective than non-directive psychotherapy or no therapy. In general, a variety of CBT approaches appear to be helpful for patients with GAD, including cognitive strategies (e.g., cognitive restructuring) and behavioural strategies (e.g., relaxation training). Although some studies have shown differences in the effectiveness of different cognitive and behavioural treatments, most studies have found few differences in the effectiveness of these approaches.

Many questions remain to be answered regarding the treatment of GAD. First, relatively few studies are based on recent criteria and it would be important for psychological and pharmacological treatments to be evaluated using properly diagnosed patients and a broad range of measures (including cognitive assessments). In addition, virtually nothing is known about the relative and combined efficacy of medications and CBT. More studies comparing these approaches should be conducted. Much more information is needed regarding the long-term impact of various treatments. Studies comparing CBT and pharmacological approaches should be designed to assess the effects of discontinuing treatment, in addition to the short-term impact of interventions. Finally, research is needed to identify methods of predicting which patients are likely to respond to particular treatments. Even if studies find that similar percentages of patients respond to various types of treatments, it is still to be determined whether it is the same patients who are likely to respond to each treatment modality.

Chapter 8

SPECIFIC PHOBIA

Introduction

Although over 50 studies have been conducted to evaluate behavioural treatments for specific phobias, the vast majority suffer from serious methodological limitations. For example, most studies are based on college student volunteers, who do not necessarily meet full criteria for specific phobia. In typical studies, participants are individuals who report fearing a specific object or situation; however, there is usually no attempt to assess the degree to which the fear causes the individual significant distress or functional impairment. Therefore, it is likely that most studies are based primarily on participants who do not actually meet full diagnostic criteria for specific phobia.

To date, no controlled studies have examined the use of pharmacotherapy for specific phobias. In fact, nearly every study has focused on exposure-based interventions, to the exclusion of other strategies (e.g., cognitive therapy, and supportive psychotherapy). It is only in the past five years that studies have begun to examine behavioural treatments for properly diagnosed individuals with specific phobias. Four such studies were found for this review. With reference to self-help (self-directed) treatments, preliminary studies suggest that these treatments may be less effective, compared to studies with PD and PDA.

Spider Phobia Studies

Öst, Salkovskis and Hellström (1991) randomly assigned 34 individuals with simple phobias of spiders (according to DSM-III-R criteria, diagnosed by structured interviews) to: (1) a single session of therapist-assisted exposure (maximum three hours); or (2) self-directed exposure using a manual over a two-week period. Using conservative composite criteria for recovery (based on clinically significant

change on behavioural testing, fear ratings, and clinician ratings), 71% of those in the therapist-assisted exposure group and six percent of those in the self-exposure treatment were considered to be clinically improved. At post-treatment, therapist-assisted exposure was superior to self-exposure on self-report measures, behavioural measures, and clinician ratings. Gains were maintained at one-year follow-up.

In a follow-up study, Hellström and Öst (1995) treated 52 spider phobic individuals meeting DSM-III-R criteria for simple phobia (based on structured interviews) in five different treatment conditions: (1) one session of therapist-assisted exposure (up to three hours); (2) specific manual-based self-exposure at home; (3) specific manual-based self-exposure at the clinic; (4) general manual-based self-exposure at home; and (5) general manual-based self-exposure at the clinic. Specific manuals explained how to overcome spider phobias by exposure, whereas the general manuals described exposure instructions for overcoming phobias in general. Following treatment and at one-year follow-up, therapist-assisted treatment was more effective than all manual-based treatments, except the specific manual-based clinic treatment. Self-treatment using a specific manual at the clinic was more effective than other manual-based treatments, and this difference reached significance at follow-up. The percentages of patients meeting criteria for clinically significant improvement were 80% for therapist-assisted exposure, 63% for specific clinic-based manual treatment, 10% for specific home-based manual treatment, 9% for general home-based manual treatment, and 10% for general clinic-based manual treatment.

Blood Phobia Studies

Öst, Fellenius, and Sterner (1991) compared five sessions of: (1) applied tension (i.e., learning to tense muscles and raise blood pressure in the presence of phobic cues); (2) exposure in vivo; and (3) tension only (without exposure to phobic cues) in 30 blood phobic patients meeting

DSM-III-R criteria for simple phobia. Assessments included self-report, behavioural, and physiological measures taken pre- and post-treatment, and repeated at one-year follow-up. All groups improved significantly and maintained their gains at follow-up. Applied tension was significantly more effective than exposure at post-treatment and follow-up. Tension alone was marginally more effective than exposure. The percentages of individuals considered clinically improved at post-treatment according to stringent criteria were 90% for applied tension, 80% for tension only, and 40% for exposure. At follow-up, the corresponding percentages were 100%, 90%, and 50%.

Hellström, Fellenius, and Öst (1996) treated 30 blood phobic individuals meeting DSM-III-R criteria for simple phobia in one of three treatments: (1) five sessions of applied tension; (2) one session of applied tension (maximum two hours); and (3) one session of tension only (maximum two hours). In addition, all patients were offered the opportunity to participate in a six-month maintenance program in which they engaged in specific self-exposure practices, recorded their progress on monitoring forms, and received feedback by telephone or letter from the therapist. All three treatments led to improvements that were maintained at follow-up. The proportions of patients at post-treatment and follow-up who were judged to be recovered were as follows: 50% and 60% for five sessions of applied tension, 0% and 70% for single session applied tension, and 30% and 60% for single session tension only. At post-treatment, five sessions of applied

tension were more effective than one session, although at follow-up there were no significant differences between groups. Self-exposure during the maintenance phase appeared important, in that 88% of those who completed the maintenance program were clinically improved at follow-up, compared to 36% of those who did not follow the maintenance program.

General Summary and Conclusions

Numerous studies have demonstrated that behaviour therapy is an effective method of decreasing phobias. However, very few studies have evaluated exposure-based treatments in patients meeting full criteria for specific phobias, despite the fact that specific phobias are among the most prevalent of the anxiety disorders. Additional studies are needed with a broader range of phobias (e.g., heights, storms, and flying) to assess the utility of behaviour therapy in these groups. For example, it remains to be shown whether different specific phobias might require a longer duration of treatment compared to other phobias. In addition, it is possible that some specific phobias that share features with panic disorder and agoraphobia (e.g., claustrophobia) might be improved using strategies that have been shown to be effective for treating panic (e.g., medications, interoceptive exposure, and cognitive therapy). Almost nothing is known about the efficacy of these approaches for different specific phobia types.

Chapter 9

POSTTRAUMATIC STRESS DISORDER

Introduction

Posttraumatic stress disorder (PTSD) is the least researched of the anxiety disorders. Few outcome studies exist for pharmacological or psychological treatments; the number of controlled studies is even fewer. Furthermore, no studies have been conducted to compare pharmacological and psychological treatments, nor have there been studies to investigate combined treatments.

Controlled studies have been conducted primarily with antidepressants and CBT. Among antidepressants, some benefits have been found with phenelzine and fluoxetine. Among psychological treatments, imaginal exposure, relaxation training, and cognitive techniques have been used with some success. However, it should be emphasized that it is still too early to know the extent to which pharmacological and psychological approaches are helpful for people affected by PTSD. In addition, a new technique called eye movement desensitization and reprocessing (EMDR) has recently become popular among some clinicians and researchers. This technique involves having a patient track a therapist's hand movements back and forth while they imagine a traumatic scene. Although uncontrolled studies have suggested that this may be helpful for patients with PTSD and other problems, critics have argued that the efficacy of this treatment can be attributed entirely to the effects of the imaginal exposure, and that there is no evidence that EMDR works any better than exposure alone (Herbert and Mueser, 1992; Lilienfeld, 1996; Lohr, Kleinknecht, Tolin, and Barrett, 1995).

Medication Studies

Six controlled studies with adequate sample sizes (at least 10 per group) were found. Davidson et al. (1990) compared amitriptyline (mean dose = 160.7 mg/day) and placebo in an eight-week treatment study involving 46 combat veterans meeting DSM-III criteria for PTSD (according to a structured interview). For the 33 patients completing eight weeks of treatment, amitriptyline was superior to placebo on four out of five measures. In general, comorbidity was associated with greater drug-placebo differences, although comorbid depression, panic disorder, and alcohol abuse were associated with worse outcomes. After eight weeks, 64% of those taking amitriptyline and 72% of those taking placebo still met PTSD criteria, a non-significant difference. In a follow-up study, Davidson et al. (1993) reported that drug response (*but not placebo response*) was predicted by lower baseline levels of depression, neuroticism, combat intensity, anxious mood, impaired concentration, somatic symptoms, feelings of guilt, and specific PTSD symptoms (intrusive and avoidant trauma symptoms). The authors conclude that these findings indicate a specific relationship between amitriptyline and measures of depression, PTSD, personality, anxiety, and intensity of combat trauma.

In an eight-week study of 60 male combat veterans with DSM-III diagnoses of PTSD (determined by a structured interview), Kosten and colleagues (Frank, Kosten, Giller, and Dan, 1988; Kosten, Frank, Dan, McDougle, and Giller, 1991) compared the efficacy of phenelzine (mean maximum dose = 68 mg/day), imipramine (mean maximum dose = 225), and placebo. Phenelzine was significantly more effective than imipramine which, in turn, was more effective than placebo. Percentage improvements in scores on the Impact of Event Scale (IES) (Horowitz et al., 1972) were 44%, 25%, and 5% for patients taking phenelzine, imipramine, and placebo,

respectively. In general, scores on the intrusion subscale of the IES changed significantly more than scores on the avoidance subscale. In contrast to this study, Shestatzky, Greenberg, and Lerer (1988) found no significant differences between phenelzine (mean dosage = 66 mg/day) and placebo in a four-week double-blind crossover study of 13 patients (10 completers) with DSM-III diagnoses of PTSD. However, relative to the Davidson et al. (1993) study (above), this study had fewer subjects and a shorter duration of active treatment. In addition, unlike the Davidson et al. study which included only combat veterans, patients in the Shestatzky et al. (1988) trial included individuals with a variety of trauma experiences which may have increased within group variability.

Reist et al. (1989) compared desipramine (mean dosage = 165 mg/day) and placebo in a four-week, double-blind crossover study with 18 combat veterans meeting DSM-III criteria for PTSD (according to structured interviews). Although desipramine led to decreases in depression, it was no more effective for symptoms of PTSD than was placebo (possibly due to the brief duration of treatment).

In contrast, five weeks of treatment with fluoxetine (mean dose = 40 mg/day) but not placebo led to significant improvement in PTSD symptoms in a mixed group of 64 patients with DSM-III-R diagnoses of PTSD (van der Kolk, et al., 1994). Changes were most pronounced in symptoms related to the arousal and numbing sub-categories. In addition, non-veteran patients responded more than did veterans.

Summary

Very little controlled research has been conducted, and the few studies that have been published have yielded conflicting results. Some studies have shown antidepressants (e.g., amitriptyline, desipramine, phenelzine) to be more effective than placebo, other studies have failed to show differences.

Psychological Treatment Studies

Studies of Combat Veterans with PTSD

Two controlled studies with adequate sample sizes (at least 10 per group) have been conducted for the behavioural treatment of combat-related PTSD. Keane, Fairbank, Caddell, and Zimering (1989) randomly assigned 24 patients with DSM-III diagnoses of PTSD to: (1) flooding treatment (14 to 16 sessions); or (2) wait-list control. Overall, behaviour therapy was significantly better than the wait-list control condition on many measures, including declines in re-experiences of the traumatic event, as well as in anxiety and depression. Numbing symptoms and social avoidance were not particularly affected by treatment.

The second study (Jensen, 1994) compared eye movement desensitization and reprocessing (EMDR) to a control condition in which patients received no formal treatment, but were permitted to seek treatment elsewhere. Patients met DSM-III-R criteria for PTSD (based on a structured interview). Overall, EMDR did not lead to significant improvement in PTSD symptoms, although it did lead to within-session decreases in anxiety.

Other Studies of PTSD Patients

Vaughan et al. (1994) studied 36 individuals with DSM-III-R diagnoses of PTSD following various traumas and based on structured interviews. Patients were randomly assigned to one of three treatment groups: (1) imaginal exposure; (2) EMDR; or (3) applied muscle relaxation. About half of the participants were assigned to a wait-list control group before beginning their treatment. Ratings were conducted by independent raters pre- and post-treatment, as well as three months following treatment. On all measures, patients showed improvement from pre- to post-treatment and gains were maintained at follow-up. Patients did not improve while on the wait-list. No significant differences emerged across the treatment groups, although the findings suggest that EMDR was more effective in reducing intrusive memories immediately after treatment than the other forms of treatment.

Edna Foa and her colleagues have published two studies of cognitive-behavioural therapy (CBT) for female assault victims with PTSD. The first study (Foa, Rothbaum, Riggs, and Murdock, 1991) randomly assigned 45 patients with PTSD to four conditions: (1) stress inoculation training (relaxation and cognitive strategies); (2) prolonged exposure; (3) supportive counselling; or (4) wait-list control. All conditions led to improvement at post-treatment and follow-up. However, stress inoculation training was superior to counselling and wait-list at post-treatment. At follow-up, prolonged exposure led to the greatest change in PTSD symptoms. In a second study, Foa, Hearst-Ikeda, and Perry (1995) compared four sessions of CBT to an assessment-only control condition in 20 recent female victims of assault. Two months later, 10% of the CBT group met DSM-III-R criteria for PTSD, whereas 70% of the control group met PTSD criteria, following evaluations by independent interviewers.

Summary

Studies of CBT have yielded promising findings, although there are still too few properly controlled studies to conclude that CBT is an effective treatment. Furthermore, none of the cognitive-behavioural strategies appears to be more effective than the others.

General Summary and Conclusions

Very little is known about the effectiveness of treatments for PTSD. With respect to medications, very little controlled research has been conducted, and the few studies that have been published have yielded conflicting results. Some studies have shown antidepressants (e.g., amitriptyline, desipramine, phenelzine) to be more effective than placebo, other studies have failed to show differences. Medication studies completed to date suffer from a variety of limitations including small sample sizes and a duration of treatment that may be too brief to be helpful.

Overall, studies of CBT have yielded more promising findings, although there are still too few studies to conclude that CBT is an effective treatment. Furthermore, none of the cognitive-behavioural strategies appears to be more effective than the others.

Areas for future research include controlled research studies of the relative and combined efficacy of pharmacological treatments and psychological treatments.

Chapter 10

CONCLUSIONS

This review provides a comprehensive examination of the controlled treatment studies in the anxiety literature over the past 15 years, identified through searches of the Medline and PsychLit data bases, and which met specific author-defined criteria. This report provides the basis for a discussion paper in which the main findings are summarized and suggestions for potential future research and implications for public awareness, professional education, and care issues are outlined.

Summary of Main Research Findings

- Across the various anxiety disorders, effective pharmacological (excluding for phobias) and cognitive-behavioural treatments have been developed and empirically validated.
- There is little consistent evidence that combining cognitive-behavioural therapy (CBT; a form of psychological treatment) and medication is any more effective than using either treatment alone.
- Panic disorder with (PDA) and without (PD) agoraphobia have been the most extensively researched disorders, whereas specific phobias and posttraumatic stress disorder (PTSD) have been associated with the fewest outcome studies meeting criteria for this review.
- Little is known about the effectiveness of most pharmacological and psychological treatments for PTSD and appropriately diagnosed specific phobias, although existing research findings are promising.

Pharmacological Treatments

- With the exception of specific phobias, certain medications (e.g., alprazolam and clomipramine) have been shown to be helpful for individuals with anxiety disorders.
- Preliminary research has shown that selective serotonin reuptake inhibitor (SSRI) antidepressants are useful for most types of anxiety problems. Controlled research studies report that the SSRIs tend to be the pharmacological treatment of choice in studies of obsessive-compulsive disorder (OCD).
- Tricyclic antidepressants appear to be most useful for people affected by PD and PDA.
- MAOI antidepressants (and reversible MAOIs) have been shown to be helpful for several disorders, and they may be the pharmacological treatment of choice for social phobia, at least until additional outcome studies are conducted with other medications.
- Benzodiazepines appear to be useful for individuals with PD, PDA, social phobia, and generalized anxiety disorder (GAD). While they bring about the desired effect more quickly than do other interventions, there are withdrawal and rebound effects associated with the discontinuation of the benzodiazepines.
- Other anxiolytics, such as buspirone, have been shown to be helpful for treating GAD, but not for the other anxiety disorders.

Psychotherapeutic Studies

- Cognitive and behavioural treatments are effective methods for decreasing symptoms in each of the anxiety disorders, although few properly controlled studies have been conducted to evaluate the effectiveness of CBT (and other psychological treatments) for PTSD and appropriately defined specific phobias.

- ◉ CBT has been shown to be more effective for anxiety disorders than other psychological treatments and is at least as effective as pharmacological approaches. For a variety of disorders, CBT appears to have more lasting effects following termination of treatment than do medications.
- ◉ Among behavioural treatments, exposure-based treatments are effective for phobic disorders as well as for PTSD and OCD. Response prevention appears to be an important component of OCD treatment as well.
- ◉ Cognitive interventions are often included in the treatment of PD, PDA, social phobia, PTSD and GAD. They are less often included in the treatment of specific phobias and OCD.

Other (Non-Drug) Interventions

- ◉ With the exception of PD and PDA, little is known about the usefulness of self-help (self-instruction) treatments (e.g., self-help books) and treatments involving minimal therapist contact (e.g., treatment by telephone).
- ◉ Preliminary studies with specific phobias suggest that self-instruction methods may be less effective, compared to studies with PD and PDA.

Potential Directions for Future Research

The quality of research varies greatly across the anxiety disorders. In the case of PD and PDA, the state of the research is quite advanced. Most studies are based on current diagnostic criteria, with patients diagnosed by structured interviews. Sample sizes are adequate and studies tend to be designed with appropriate controls and include measures of treatment integrity. Numerous studies have been conducted with a range of medications, cognitive-behavioural treatments, combined treatments, and self-administered treatments. In contrast, the other anxiety disorders have not been studied as thoroughly.

Based on the findings of this review of the literature, areas for potential investigation on treatment of the anxiety disorders include:

- ◉ Longitudinal research, using multidimensional approaches, is needed regarding risk factors for developing anxiety disorders. This is especially the case for disorders other than PD and PDA. In addition, there are virtually no studies that have examined the role of protective factors that might decrease the tendency to develop anxiety disorders among those considered to be at risk.
- ◉ More controlled research, including meta-analytic studies, is needed on the relative and combined short- and long-term efficacy of pharmacological and psychological treatments for PTSD, specific phobias, social phobia and GAD.
- ◉ Methodologically-sound research on the effectiveness of other forms of psychotherapeutic approaches (e.g., psychodynamic and humanistic approaches) for the treatment of anxiety disorders is needed.
- ◉ Studies exploring treatment sequencing (i.e., the order in which different treatment components should be introduced) are needed in cases where combined treatments approaches are used.
- ◉ Long-term follow-up treatment studies are needed to explore possible differences in treatment efficacy over time (e.g., initial differences between treatments may wash out over time).
- ◉ More controlled research is needed to evaluate the effectiveness of newer SSRI's and other antidepressant medications in the treatment of the anxiety disorders.
- ◉ Treatment studies should include a broader range of outcome variables such as impact of anxiety disorders on quality of life, future health care utilization costs, lost wages, reduced productivity at work, and impact of treatment on families (including children).

- ◉ More data are needed on predictors of treatment response, as well as mechanisms by which treatments work, for all of the anxiety disorders. Once the efficacy of these treatments is established for different groups of patients, it will be important to find ways of predicting which treatments are likely to be effective for particular individuals, including those with one or more comorbid conditions, and to disseminate this information to clinicians and to the public.
- ◉ Virtually nothing is known about the effectiveness of treatment for the anxiety disorders by non-mental health professionals (e.g., family doctors). A variety of treatment manuals and training workshops have become available in the past few years, and it would be useful to assess the extent to which general practitioners can be trained to administer medications and CBT for anxiety disorders.
- ◉ Given the effectiveness of self-help (self-instruction) treatments and treatments involving minimal therapist contact for PD and PDA, it seems worthwhile to conduct more research on these approaches for other anxiety disorders.
- ◉ Controlled research studies as to the role and effectiveness of self-help/mutual aid approaches (e.g., participation in self-help groups) in helping individuals to cope with anxiety disorders should be undertaken. Preliminary research and anecdotal evidence suggest that many individuals (and their families) find participation in self-help groups beneficial.
- ◉ Although a critical review of measurement tools for the anxiety disorders was beyond the scope of this review, evaluation of these instruments is an important area for future research. A compendium and critical review of these instruments could be a useful first step to addressing this issue. (A list of useful references in the area of anxiety assessment tools is included in Appendix 3 for interested readers).

Because the state of the research varies for each of the anxiety disorders, some research recommendations may be identified which are specific to each type of disorder. These include:

Panic Disorder with and without Agoraphobia:

- ◉ More research is needed on the effects of various forms of treatment in specific populations, including the elderly, children, culturally diverse groups, and individuals with multiple psychological problems (e.g., anxiety disorders and substance abuse).

Obsessive-Compulsive Disorder:

- ◉ Research on psychosocial interventions (e.g., exposure, response prevention, and cognitive therapy) is needed. More needs to be learned regarding the process of therapeutic change.
- ◉ Many of the older, uncontrolled studies should be repeated, using appropriate controls, adequate sample sizes, diagnosis using DSM-IV criteria (as measured by structured interviews), and adequate long-term follow-up.

Social Phobia:

- ◉ Further research is needed to confirm preliminary research findings that CBT is at least as effective as pharmacological approaches in the short-term and probably more effective than medications in the long-term.
- ◉ The role of self-help approaches in social phobia remains to be studied.

Generalized Anxiety Disorder:

- ◉ Since relatively few studies are based on recent criteria, it is important for psychological and pharmacological treatments to be evaluated using properly diagnosed patients and a broad range of measures (including cognitive assessments).

Specific Phobia:

- Studies that explore the efficacy of behaviour therapy with a broader range of diagnosed phobias (e.g., heights, storms, flying, et cetera) are needed.

- The efficacy of using strategies (e.g., medications, interoceptive exposure) shown to be effective for treating panic disorder for different specific phobia types remains to be investigated.

Implications for education and other related activities, designed to contribute to improved treatment of the anxiety disorders, are outlined in the accompanying discussion paper, “Anxiety Disorders: Future Directions for Research and Treatment”.

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Chapter 5: Obsessive-Compulsive Disorder

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Appendix 1:

- Bland, R.C., Orn, H., and Newman, S.C. (1988). Lifetime prevalence of psychiatric disorders in Edmonton. *Acta Psychiatrica Scandinavica*, *77(Suppl. 338)*, 24-32.
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Appendix 4:

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A p p e n d i x 1

Lifetime Prevalence of the Anxiety Disorders (%)

Disorder	ECA Study*	NCS Study	Edmonton Study
Panic Disorder	0.9	3.5	1.2
Agoraphobia	4.2	5.3	2.9
OCD	—	—	3.0
Social Phobia	2.8	13.3	1.7
GAD	—	5.1	—
Specific Phobia	11.2	11.3	7.2
PTSD	—	7.8	—
Any AD	10.4-25.1*	24.9	11.2

* based on three of the five ECA sites

OCD: obsessive-compulsive disorder; GAD: generalized anxiety disorder; PTSD: posttraumatic stress disorder; ECA Study: Epidemiological Catchment Area Study (Bourdon et al., 1988; Robins et al., 1984); NCS: National Comorbidity Survey (Kessler et al., 1994); Edmonton Study: refers to the prevalence study conducted by Bland et al., 1988.

Explanatory note:

Discrepancies in survey findings have been attributed to (in the ECA and Edmonton surveys) the standardization of prevalence rates to the census population of each site instead of to an identical population (Bland et al., 1988), and to variation in survey questions and interviewer instructions (Robins et al., 1984). Kessler et al. (1994) indicate that the higher prevalence rates in the NCS than in the other two surveys can, in part, be attributed to a number of methodological factors including: use of a national sample, focus on a younger age range (15-54 years), use of a correction weight to adjust for nonresponse bias, and use of DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, 3rd Revised Edition) (as opposed to DSM-III) criteria. Although the instrument used in the NCS (the Composite International Diagnostic Interview or CIDI; Robins, Wing, Wittchen, and Helzer, 1988) is similar to the instrument used in the ECA study (the Diagnostic Interview Schedule or DIS; Robins, Helzer, Croughan, and Ratcliff, 1981), Kessler et al. suggest that differences in wording and depth of probing in the NCS could have contributed to higher prevalence estimates.

A p p e n d i x 2

Diagnostic Criteria for Panic Attacks, Agoraphobia, and the Anxiety Disorders²

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Panic Attack

Note: A Panic Attack is not a codable disorder. Code the specific diagnosis in which the Panic Attacks occur (e.g., 300.21 Panic Disorder with Agoraphobia).

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

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

Agoraphobia

Note: Agoraphobia is not a codable disorder. Code the specific disorder in which the Agoraphobia occurs (e.g., 300.21 Panic disorder with Agoraphobia or 300.22 Agoraphobia without History of Panic Disorder).

- A. Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed Panic Attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in a line; being on a bridge; and travelling in a bus, train or automobile.
Note: Consider the diagnosis of Specific Phobia if the avoidance is limited to one or only a few specific situations, or Social Phobia if the avoidance is limited to social situations.
- B. The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a Panic Attack or panic-like symptoms, or require the presence of a companion.
- C. The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as Social Phobia (e.g., avoidance limited to social situations because of fear of embarrassment), Specific Phobia (e.g., avoidance limited to a single situation like elevators), Obsessive-Compulsive Disorder (e.g., avoidance of dirt in someone with an obsession of contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe stressor), or Separation Anxiety Disorder (e.g., avoidance of leaving home or relatives).

Panic Disorder without Agoraphobia (300.01)

- A. Both (1) and (2):
- (1) recurrent unexpected panic attacks
 - (2) at least one of the attacks has been followed by one month (or more) of one (or more) of the following:
 - a) persistent concern about having additional attacks
 - b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, “going crazy”)
 - c) a significant change in behaviour related to the attacks
- B. Absence of Agoraphobia.
- C. The Panic Attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
- D. The Panic Attacks are not better accounted for by another mental disorder, such as Social Phobia (e.g., occurring on exposure to feared social situations), Specific Phobia (e.g., on exposure to a specific phobic situation), Obsessive-Compulsive Disorder (e.g., on exposure to dirt in someone with an obsession about contamination), Post-Traumatic Stress Disorder (e.g., in response to stimuli associated with a severe stressor), or in Separation Anxiety Disorder (e.g., in response to being away from home or close relatives).

Panic Disorder with Agoraphobia (300.21)

- A. Both (1) and (2):
- (1) recurrent unexpected panic attacks
 - (2) at least one of the attacks has been followed by one month (or more) of one (or more) of the following:
 - a) persistent concern about having additional attacks
 - b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, “going crazy”)
 - c) a significant change in behaviour related to the attacks
- B. The presence of Agoraphobia.
- C. The Panic Attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
- D. The Panic Attacks are not better accounted for by another mental disorder, such as Social Phobia (e.g., occurring on exposure to feared social situations), Specific Phobia (e.g., on exposure to a specific phobic situation), Obsessive-Compulsive Disorder (e.g., on exposure to dirt in someone with an obsession about contamination), Post-Traumatic Stress Disorder (e.g., in response to stimuli associated with a severe stressor), or in Separation Anxiety Disorder (e.g., in response to being away from home or close relatives).

Obsessive-Compulsive Disorder (300.3)

mental acts are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

A. Either obsessions or compulsions:

Obsessions are defined by (1), (2), (3), and (4):

- (1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
- (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems
- (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
- (4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

Compulsions are defined by (1) and (2):

- (1) repetitive behaviours (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to certain rules that must be applied rigidly
- (2) the behaviours or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviours or

- B. At some point during the course of the disorder, the person has recognised that the obsessions or compulsions are excessive or unreasonable. **Note:** This does not apply to children.
- C. The obsessions or compulsions cause marked distress, are time consuming (take more than one hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.
- D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).
- E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

- ◉ **With Poor Insight:** if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable.

Social Phobia (300.23)

- A. Marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. **Note:** In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.
- B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed Panic Attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking away from social situations with unfamiliar people.
- C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent.
- D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.
- E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.
- F. In individuals under age 18 years, the duration is at least 6 months.
- G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., Panic Disorder With or Without Agoraphobia, Separation Anxiety Disorder, Body Dysmorphic Disorder, a Pervasive Developmental Disorder, or Schizoid Personality Disorder).
- H. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of Stuttering, trembling in Parkinson's disease or exhibiting abnormal eating behaviour in Anorexia Nervosa or Bulimia Nervosa.

Specify if:

- ◉ **Generalized:** if the fears include most social situations (also consider the additional diagnosis of Avoidant Personality Disorder).

Generalized Anxiety Disorder (300.02)

- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
- B. The person finds it difficult to control the worry.
- C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months).

Note: Only one item is required in children.

- (1) restlessness or feeling keyed up or on edge
- (2) being easily fatigued
- (3) difficulty concentrating or mind going blank
- (4) irritability
- (5) muscle tension
- (6)

sleep disturbance (difficulty falling or staying sleep, or restless unsatisfying sleep)

- D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety and worry is not about having a Panic Attack (as in Panic Disorder), being embarrassed in public (as in Social Phobia), being contaminated (as in Obsessive-Compulsive Disorder), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in Anorexia Nervosa), having multiple physical complaints (as in Somatization Disorder), or having a serious illness (as in Hypochondriasis), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.
- E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

Posttraumatic Stress Disorder (309.81)

- A. The person has been exposed to a traumatic event in which both the following were present:
- (1) the person experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
 - (2) the person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behaviour
- B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
- (1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed
 - (2) recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content
 - (3) acting or feeling as if the traumatic event was recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur
 - (4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
 - (5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
- C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
- (1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
 - (2) efforts to avoid activities, places or people that arouse recollections of the trauma
 - (3) inability to recall an important aspect of the trauma
 - (4) markedly diminished interest or participation in significant activities
 - (5) feeling of detachment or estrangement from others
 - (6) restricted range of affect (e.g., unable to have loving feelings)
 - (7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)
- D. Persistent symptoms of increased arousal (not present before the trauma) as indicated by two (or more) of the following:
- (1) difficulty falling or staying asleep
 - (2) irritability or outbursts of anger
 - (3) difficulty concentrating
 - (4) hypervigilance
 - (5) exaggerated startle response
- E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.
- F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

- ◉ **Acute:** if duration of symptoms is less than 3 months
- ◉ **Chronic:** if duration of symptoms is 3 months or more

Specify if:

- ◉ **With Delayed Onset:** if onset of symptoms is at least 6 months after the stressor.

Specific Phobia (300.29)

- A. Marked and persistent fear that is excessive or unreasonable, cued by the presence (or anticipation) of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).
- B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or situationally predisposed Panic Attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or clinging.
- C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent.
- D. The phobic situation(s) is avoided or else is endured with intense anxiety or distress.
- E. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.
- F. In individuals under age 18 years, the duration is at least 6 months.
- G. The anxiety, Panic Attacks, or phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder, such as Obsessive-Compulsive Disorder (e.g., fear of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe stressor), Separation Anxiety Disorder (e.g., avoidance of school), Social Phobia (e.g., avoidance of social situations because of fear of embarrassment), Panic Disorder With Agoraphobia, or Agoraphobia Without History of Panic Disorder.

Specify type:

- ◉ **Animal Type**
- ◉ **Natural Environment Type** (e.g., heights, storms, water)
- ◉ **Blood-Injection-Injury Type**
- ◉ **Situational Type** (e.g., airplanes, elevators, enclosed places)
- ◉ **Other Type** (e.g., phobic avoidance of situations that may lead to choking, vomiting, or contracting an illness; in children, avoidance of loud sounds or costumed characters)

A p p e n d i x 3

Useful references relating to assessment of anxiety disorders

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Greist, J.H., Kobak, K.A., Jefferson, J.W., Katzelnick, D.J., and Chene, R.L. (1995). The clinical interview. In R.G. Heimberg, M.R. Liebowitz, D.A. Hope, and F.R. Schneier (Eds.), *Social phobia: Diagnosis, assessment and treatment*. New York: Guilford

Generic Name	Brand Name	Type of Medication
Adinazolam	Deracyn	Benzodiazepine* ³
Alprazolam	Xanax	Benzodiazepine
Brofaromine	Experimental	Reversible MAOI (Type A)*
Bupirone	Buspar	Azospirodecanedione
Carbamazepine	Tegretol	Anticonvulsant
Clomipramine	Anafranil	SSRI Antidepressant
Clonazepam	Rivotril	Benzodiazepine
Clonidine	Dixarit	Alpha-2 Adrenergic agonist
Diazepam	Valium	Benzodiazepine
Dixyrazine	Esucos	Neuroleptic*
Fluvoxamine	Luvox	SSRI Antidepressant
Imipramine	Tofranil	Tricyclic Antidepressant
Inositol	Linodil	Isomer of Glucose
L-365,260	Experimental	CCK _B Antagonist*
Lofepamine	Gamonil	Tricyclic Antidepressant*
Lorazepam	Ativan	Benzodiazepine
Paroxetine	Paxil	SSRI Antidepressant
Propranolol	Inderal	Beta Blocker
Trazodone	Desyrel	Antidepressant
Zimeldine	Zelmid	SSRI Antidepressant ⁴

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s, B., and Turk, C.L. (1995). Behavioural assessment: Self-report, physiology, and overt behaviour. In R.G. Heimberg, M.R. Liebowitz, D.A. Hope, and F.R. Schneier (Eds.), *Social phobia: Diagnosis, assessment and treatment*. New York: Guilford Publications.

Shear, M.K., and Maser, J.D. (1994). Standardized assessment for panic disorder research: A conference

Generic Name	Brand Name	Type of Medication
Buspirone	Buspar	Azospirodecanedione
Clonidine	Catopress or Dixarit	Alpha-2 Adrenergic Agonist
Clomipramine	Anafranil	SSRI Antidepressant
Clonazepam	Rivotril	Benzodiazepine
Clorgyline	Experimental	MAOI Antidepressant*
Desipramine	Pertofran or Norpramin	Tricyclic Antidepressant
Diphenhydramine	Benadryl	Antihistamine [Control Drug (with side effects)]
Fluoxetine	Prozac	SSRI Antidepressant
Fluvoxamine	Luvox	SSRI Antidepressant
Haloperidol	Haldol	Neuroleptic
Imipramine	Tofranil	Tricyclic Antidepressant
Lithium Carbonate	Lithane or Carbolith	Mood Stabilizer
Nortriptyline	Pamelor or Aventyl	Tricyclic Antidepressant
Phenelzine	Nardil	MAOI Antidepressant
Sertraline	Zoloft	SSRI Antidepressant

report. *Archives of General Psychiatry*, 51, 346-354.

Generic Name	Brand Name	Type of Medication
Alprazolam	Xanax	Benzodiazepine
Atenolol	Tenormin	Beta Blocker
Brofaromine	Experimental	Reversible MAOI(Type A)*
Clonazepam	Rivotril	Benzodiazepine
Moclobemide	Manerix	Reversible MAOI (Type A)
Phenelzine	Nardil	MAOI Antidepressant
Sertraline	Zoloft	SSRI Antidepressant

Taylor, S. (1995). Assessment of obsessions and compulsions: Reliability, validity and sensitivity to treatment effects. *Clinical Psychology Review*, 15, 261-296.

Watson, C.G. (1990). Psychometric posttraumatic stress disorder measurement techniques: A review.

Generic Name	Brand Name	Type of Medication
Alpidem	Ananxil	Non-benzodiazepine anxiolytic* ⁵
Alprazolam	Xanax	Benzodiazepine
Bromazepam	Lectopam	Benzodiazepine
Buspirone	Buspar	Azospirodecanedione
CGP 361A	_____ ⁶	Beta Blocker*
Chlorprothixene	Tarasan	Antipsychotic*
CI-988	Experimental	CCK _B Antagonist*
Clobazam	Frisium	Benzodiazepine
Clorazepate	Tranxene	Benzodiazepine
Diazepam	Valium	Benzodiazepine
Etizolam	Pasaden	Benzodiazepine*
Flupenthixol	Fluanxol	Neuroleptic
Imipramine	Tofranil	Tricyclic Antidepressant
Ipsapirone	Experimental	Azapirone*
Lorazepam	Ativan	Benzodiazepine
Trazodone	Desyrel	Tricyclic Antidepressant
Trifluoperazine	Stelazine	Neuroleptic

Psychological Assessment: A Journal of Consulting and Clinical Psychology, 2, 460-469.

Generic Name	Brand Name	Type of Medication
Amitriptyline	Elavil	Tricyclic Antidepressant
Desipramine	Norpramin	Tricyclic Antidepressant
Fluoxetine	Prozac	SSRI Antidepressant
Imipramine	Tofranil	Tricyclic Antidepressant
Phenelzine	Nardil	MAO Inhibitor

APPENDIX 4

CBT	Cognitive-Behavioural Therapy
CCK	Cholecystokinin
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECA	Epidemiological Catchment Area
EMDR	Eye Movement Desensitization and Reprocessing
GABA	Gamma Amino-Butyric Acid
GAD	Generalized Anxiety Disorder
OCD	Obsessive-Compulsive Disorder
PD	Panic Disorder
PDA	Panic Disorder with Agoraphobia
PTSD	Posttraumatic Stress Disorder
RDC	Research Diagnostic Criteria
SCID	Structured Clinical Interview for DSM-III-R
SSRI	Selective Serotonin Reuptake Inhibitor

Glossaries

Glossary of Medications

Panic Disorder and Agoraphobia

Analytic Psychotherapy	A form of psychotherapy based on the methods described by Freud and others. Psychological problems are assumed to stem from deep-rooted intrapsychic conflicts. Therapy helps the patient to develop insight into possible original causes of his or her problem, which presumably leads to improvement in symptoms.
Anti-Exposure Instructions	A control treatment sometimes used in studies of exposure therapy. Individuals receiving anti-exposure instructions are told not to engage in exposure to feared objects or situations.
Anxiety Management Training	A form of CBT described by Butler et al. (1984) for the treatment of social phobia. This treatment includes such techniques as relaxation, distraction, and rational self-talk.
Applied Relaxation Training	A form of relaxation training in which muscle relaxation is taught in the context of in vivo exposure therapy. Individuals are taught to relax their muscles while being exposed to increasingly frightening situations.
Applied Tension	A method of treating individuals with blood or injection phobias who tend to faint in the feared situation. Individuals are taught to tense the muscles of their body in order to raise their blood pressure and thereby prevent fainting in the presence of blood or injections. These skills are integrated with exposure to feared cues as they are practised while confronting increasingly difficult situations.
Assertiveness Training	A form of skills training in which individuals are taught to make their needs known to others while still considering the rights of the other individual. People are taught to replace passive and aggressive communication styles with clear communication that includes specific requests, but are not hostile.
Between-Groups Design	A research design in which individuals are assigned to different groups (e.g., two different treatments) and compared on one or more measures.
Bibliotherapy	A method through which individuals use written self-help instructions or a self-help book to overcome their problems.
Breathing Retraining	A form of behavioural treatment used primarily in patients with panic disorder. Patients are taught to breathe from their diaphragm, slow down their breathing, and use meditation strategies to relax when anxious.
Classical Conditioning	A learning process believed to cause the onset of phobias in some individuals. A previously neutral stimulus is paired with a frightening stimulus, so that the neutral object becomes feared. For example, an individual who is bitten (frightening stimulus) by a dog (previously neutral stimulus) may learn to fear dogs.
Client-Centered Psychotherapy	A non-directive form of psychotherapy in which the primary intervention involves reflecting upon the individual's thoughts and feelings in order to facilitate insight into his or her problems.

Cognitive-Behavioural Therapy	A form of psychological treatment that attempts to change the thoughts or behaviours which help to maintain a psychological disorder. Examples of cognitive therapy techniques include cognitive restructuring, and coping self-statements (described below). Behavioural strategies include exposure therapy, applied relaxation training, and a variety of other techniques (described below).
Cognitive Restructuring	A component of cognitive therapy in which individuals are taught to identify and change their anxious or depressive thoughts, beliefs, predictions, and interpretations. Rather than assuming their beliefs are true, individuals are taught to consider alternative beliefs and to evaluate the evidence in a systematic and realistic way.
Comorbidity	Refers to the presence of two or more diagnoses.
Completer Analysis	Refers to treatment outcome analyses in which only individuals who completed treatment are included. Assuming that people who drop out of treatment do not respond as well as those who remain in treatment, completer analyses may overestimate the efficacy of a particular treatment.
Coping Self-Statements	A form of cognitive therapy in which individuals replace negative, anxious statements with more positive and realistic statements. For example, an individual with panic disorder who believes that he or she is dying during a panic attack, might be instructed to say to his or herself, "I have felt this way many times before and have never died."
Crossover Design	A research design in which each individual receives all treatments and therefore serves as his or her own control. For example, in a study comparing two medications, all participants would receive each medication in sequence (usually in random order). Advantages of this design over between-groups design include fewer participants and reduction of error due to individual differences. A disadvantage is the possibility of carry-over effects from one treatment to the next.
DSM Nosology	Published by the American Psychiatric Association, the DSM Nosology has been the accepted standard for psychiatric diagnoses in North America for many decades. The most recent version is DSM-IV (published in 1994). The DSM involves assessment on five axes, each of which refers to a different domain of information. Axis I refers to clinical disorders and other conditions that may be a focus of clinical attention. Axis II refers to personality disorders and mental retardation. Axis III is used to code medical conditions. Axis IV describes psychosocial stressors and environmental problems, and Axis V is used to make a global assessment of the patient's social and occupational functioning.
Dismantling Study	A study examining the relative efficacy of different combinations of treatment components (e.g., cognitive therapy versus relaxation versus combined treatment).
Double-Blind Study	A study in which neither patient nor therapist (or independent evaluator) are aware of which treatment a particular patient received. This design protects against patient and investigator biases and is most often used in pharmacological trials.

3 * denotes unavailability of medication in Canada.

4 This medication has been withdrawn from the market world-wide.

Effect Size	Refers to the magnitude of differences between groups. Although tests of statistical significance tell how likely a result was simply due to chance, effect size estimates can be used to estimate clinical significance of a particular finding.
End-point Analysis	Refers to treatment outcome analyses in which all individuals (dropouts and completers) are included. Data from dropouts are collected at the point at which they leave the study. Because this approach assumes that dropouts would not have continued to improve if they had remained in treatment, end-point analyses may underestimate the efficacy of a particular treatment.
Exposure and Response Prevention	A behavioural method used to treat obsessive-compulsive disorder. Individuals are exposed to feared stimuli (e.g., contaminated objects) and are prevented from engaging in compulsive rituals (e.g., washing).
Exposure Therapy	A form of behaviour therapy in which individuals are required to confront the object or situation that they fear. Typically, exposure is conducted in a structured and predictable manner and is repeated frequently.
Eye Movement Desensitization and Reprocessing	A new form of exposure therapy that has been a source of controversy in the behaviour therapy literature. While visualizing a feared image, individuals track the rapid movements of a therapist's finger back and forth across the image. Proponents of this approach believe that this is a unique therapeutic modality. Critics argue that the effects of this technique are attributable entirely to the exposure component.
Flooding	A form of exposure therapy in which individuals confront the feared situation or object in real life (as opposed to imaginal exposure).
Graduated Exposure	A form of exposure conducted gradually, such that individuals confront feared situations beginning with less frightening situations and progressing to more frightening situations.
Guided Mastery Therapy	A form of behavioural treatment used by Hoffart (1995) to treat panic disorder with agoraphobia in which individuals are taught to use in vivo exposure and to behave less defensively in feared situations.
Imaginal Exposure	A form of exposure therapy in which individuals confront feared objects and situations in imagination only.
Informational Fear Onset	A method of developing a fear in which fear is increased after receiving information (or misinformation) that a particular object or situation is dangerous. Examples include developing a fear of flying after reading about airplane accidents or developing a fear of heights after being told repeatedly that situations involving heights are dangerous.
Interoceptive Exposure	A component of behavioural treatment for panic disorder in which individuals conduct specific exercises designed to induce feared sensations (e.g., racing heart, dizziness, breathlessness, etc.) until the sensations are no longer feared. Typical exercises include hyperventilation, spinning, aerobic exercise, breathing through a straw, and others.

Obsessive-Compulsive Disorder

In Vivo Exposure	See Flooding .
Latin-Square Design	A research design in which multiple treatments are received in such a way that the effects of each possible treatment order can be analyzed separately.
Massed Exposure	A form of exposure therapy in which exposure practices are spaced closely together. Evidence suggests that massed exposure is more effective than exposure practices spaced farther apart in time.
Meta-Analysis	A statistical procedure in which the effects of particular treatments are estimated and pooled across a range of different studies.
Non-directive psychotherapy	A form of psychotherapy in which specific behavioural instructions are not given to patients. Typically, non-directive therapies do not include homework assignments and are focused on helping the individual to gain insight into their problems, rather than changing specific behaviours.
Operant Conditioning	A learning process believed to contribute to the maintenance of phobias in some individuals. According to operant conditioning theories, behaviours that are rewarded are likely to recur, whereas behaviours that are punished are less likely to recur. For example, avoidance behaviour is hypothesized to be maintained by the relief that an individual experiences when the feared stimulus is not present.
Paradoxical Intention	A behavioural technique in which individuals are instructed to do the exact opposite of what makes sense to them. For example, individuals with phobias might be instructed to confront the situations that they want to avoid (see Exposure Therapy).
Progressive Muscle Relaxation	A method of decreasing anxiety (especially in generalized anxiety disorder) by learning to tense and relax various muscle groups.
Rational-Emotive Therapy	A form of cognitive therapy in which individuals learn to identify and change irrational beliefs that contribute to their anxiety.
Regression to the Mean	The process by which extreme values on a particular measure tend to revert back to values closer to the average, due to chance. For example, because individuals tend to present for treatment when their symptoms are at their worst, it is not surprising that symptoms might improve somewhat over time, just by chance, regardless of treatment.
Self-Exposure Instructions	A form of exposure therapy in which individuals are instructed to engage in exposure practices on their own, not accompanied by the therapist.

Social Phobia

Self-Help	Self-help is a form of mutual aid in which groups of individuals with common problems or experiences seek to help each other through offering emotional support and practical assistance (Romeder, 1993). Self-help can be an important supplement to professional care and is a natural extension or replacement from close friends, family members, or members of the clergy.
Self-Help Groups	Voluntary self-help groups are run by and for group members. These groups provide, free of charge, educational seminars, one-to-one exchanges, informal meetings, and sharing of personal experiences.
Self-Statement Training	See Coping Self-Statements .
Social Skills Training	A group of techniques for teaching individuals (e.g., with social phobia) to improve social skills (e.g., communication, assertiveness, eye contact, and body language).
Stress Inoculation Training	A form of cognitive-behavioural therapy which includes relaxation training as well as certain cognitive strategies (e.g., coping self statements).
Structured Diagnostic Interview	An interview which asks specific questions about each symptom included in the diagnostic criteria for particular disorders. Unlike open-ended clinical interviews, the interviewer is required to read the questions verbatim.
Supportive Counseling	A form of psychotherapy in which the therapist does not provide specific behavioural instructions, but rather offers support and encouragement. Client-centered therapy is considered by some to be an example.
Supportive Psychotherapy	See Supportive Counseling .
Vicarious Conditioning	A method of developing a fear of a particular situation by observing another individual behave fearfully in the situation or by observing an individual experience a trauma in the situation.

Generalized Anxiety Disorder

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Posttraumatic Stress Disorder

5 No longer marketed anywhere in the world.

6 Information unavailable on this compound.

Glossary of Abbreviations

Glossary of Technical Terms
