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**Predictors of Response to Dexfenfluramine in a Bulimic
Population**

Marilyn Theresa Keyes

**A Thesis submitted to the Faculty of Graduate Studies and
Research in the partial fulfillment of the requirements
for the degree of
Master of Arts**

**Department of Psychology
Carleton University
August 1995**

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**"Predictors of Response to Fenfluramine in a Bulimic
Population"**

submitted by Marilyn Theresa Keyes, B.A.
in partial fulfillment of the requirements for
The degree of Master of Arts

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Abstract

Diet history characteristics were investigated as possible predictors of response to dextfenfluramine. Eighty patients with bulimia nervosa were randomly assigned to receive dextfenfluramine (30 mg) or placebo for two weeks under double-blind conditions. The Eating Disorders Inventory, the Hopkins 90-item Symptom Checklist Revised, the Beck Depression Inventory, and the Weekly Bulimic Symptom Checklist were administered one week prior to drug administration to establish a baseline, after one and two weeks of dextfenfluramine, and one week post-treatment. Subjects completed the Daily Binge Record for one week prior to and during the two weeks of drug treatment. Measures of the severity, duration, and preferred style of dieting from the Diagnostic Schedule of Eating Disorders completed during assessment were investigated as possible predictors of response to dextfenfluramine. Results indicate that a specific serotonergic agonist is effective in reducing bingeing and purging, but not the psychological and cognitive symptoms of bulimia, suggesting that direct alteration of central food intake regulatory centers modifies bulimic behaviour. Diet history, as measured in this study, did not predict response to dextfenfluramine.

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In 1976 the American Psychological Association included Bulimia Nervosa in the DSM-III as a distinct diagnostic entity - a specific syndrome of disordered eating. It is characterized by recurrent episodes of binge eating, on average a minimum of two episodes a week for at least three months, accompanied by a feeling of lack of control over eating during the binge. A persistent overconcern with body shape and weight is present and efforts to avoid weight gain are made via self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise.

The frequency of binge-eating episodes can range from one to forty-six episodes per week. Preferred binge foods are generally sweet or salty carbohydrates, and are usually foods that are regarded as "forbidden". Caloric content of binges can range from 1,200 to 11,500 calories. Binges usually occur when the individual is alone, and frequently during the evening hours. (Johnson & Connors, 1987).

Self-induced vomiting, as the most common form of purging, is engaged in by approximately 88% (see Mitchell, Specker, & de Zwaan, 1991 for a review) of bulimics. This act is usually performed as soon as possible after eating to minimize the absorption of food. It decreases the physical discomfort and reduces post-binge anxiety. This anxiety-reducing behaviour may be so reinforcing as to become pleasurable, and binges may then occur in order to vomit, or

vomiting may occur after eating a small amount of food. At the same time, feelings of disparagement and depression often follow a purging episode and a feeling that life is dominated by conflicts about eating is often present.

Laxative abuse, a relatively ineffective method of avoiding calorie absorption, has at one time or another been employed by 60.6% of bulimic patients. Laxatives are taken on a daily basis by 19.7%. The resultant temporary fluid loss gives patients a sense of weight loss, however reflex fluid retention and weight gain lead to further usage and eventual tolerance. Reports of taking 60 or more tablets daily instead of a customary dose of 1 or 2 tablets are not uncommon (see Mitchell et al., 1991 for a review).

Fifty percent of bulimic patients report having tried diuretics at least once, but only 10% use them on a daily basis. Diet pills have been experimented with by 33.9% but only 3.4% continue taking them since they are relatively ineffective as a weight-control technique and do not provide an immediate sensation of weight loss (see Mitchell et al., 1991 for a review).

Other purging behaviours include excessive exercise, chewing and spitting out food without swallowing it, and excessive use of enemas. A very dangerous but effective method of weight loss practised by patients with diabetes mellitus is neglect of insulin requirements.

Under the current criteria, approximately 4.5% of the

female, and 0.4% of the male population, have, or have had a history of bulimia. The typical bulimic is a white female between 14 and 40 years of age (Fairburn & Beglin, 1990). This disorder is at least 10 times more prevalent than the best known eating disorder, anorexia nervosa (Kaye, 1992). Age of onset of binge eating is usually in the late teens, with vomiting beginning one year later. A history of being overweight and weekly 24-hour fasting is common. There is often a previous minor episode of anorexia nervosa, but when the individual is unable to continue to suppress her hunger, she gives way to voracious eating. The resultant weight gain is of grave concern, and a morbid fear of fatness drives her to renewed efforts to restrict her eating. Efforts to maintain a weight below a self-imposed threshold level that is often below her original healthy weight give rise to persistent cravings for food. She eventually gives in to these cravings and gorges herself. Desperate efforts to control her weight lead to purgative methods.

Bulimic symptoms often develop within one and one-half years of commencement of dieting (Johnson et al., 1984) and the most frequent antecedent of bingeing behaviour is severe dieting (Halmi, 1992). It has been proposed that binge eating is a reaction to prolonged restrictive eating in the pursuit of or maintenance of a body weight which is sub-optimal (Robinson, Checkley & Russell, 1985). Other precipitants of the syndrome are traumatic events such as

loss or separation from a significant person, and difficulty in handling specific emotions, especially depression, loneliness, boredom, and anger (Johnson & Connors, 1987).

Factors commonly cited as precipitants of bulimic episodes are tension and anxiety, eating something, being alone, craving specific foods, thinking of food, going home, and feeling bored and lonely. Feeling tense and anxious is almost universally endorsed. Most patients report relief from anxiety during the binge followed by feelings of guilt. The process of vomiting results in feelings of relief, followed by a deterioration in mood (Johnson & Connors, 1987).

The psychopathological characteristics of eating-disordered patients include low self-esteem, self-regulatory deficits, body-image disturbance, mood disorder, cognitive distortions, boundary disturbance, separation/individuation fears, and a tendency to be perfectionistic, compliant and distrustful (Johnson & Connors, 1987). Bulimics typically exhibit interoceptive awareness disturbances. They have difficulty identifying and articulating a variety of internal states such as hunger, satiety, and affects. Perfectionistic thinking leads to extreme body dissatisfaction and an exaggerated drive for thinness. Bulimics score high on measures of ineffectiveness, and generally feel helpless and out of control.

Certain cognitive distortions characterize bulimia

nervosa and possibly play an important role its development and maintenance (Butow, Beumont, & Touyz, 1993). Black and white thinking leads to a view of the self and the world in terms of extremes. Foods are viewed as "good" (low calorie) or "bad" (high calorie) and when the bulimic is in control (only eats good food) she is good, but one bite of forbidden food and she has failed and is bad - and since she has "blown it" she might as well continue eating. The loss of control is viewed as loathsome weakness. Consequently bulimics most often have a negative view of themselves.

Bulimics often have an external locus of control and may invest power in food itself. They view their emotions as potentially overwhelming and destructive and attempt to relinquish responsibility for their own feelings. At the same time, they often assume responsibility for the happiness of others, which contributes to their sense of helplessness. They magnify the significance of events and states and overgeneralize negative events extending them to all aspects of life and self. These cognitive distortions generate feelings of depression and low self-esteem (Johnson & Connors, 1987).

Bulimia nervosa has been associated with high rates of other psychiatric disorders. Affective disorders, chemical dependency problems, anxiety disorders, and personality disorders often coexist with the eating disorder. The most common comorbidity is affective disorder and bulimia. The

relationship between these disorders is unclear. It has been proposed that bulimia is a variant of depression (Pope et al., 1983). An equally plausible hypothesis is that the affective disorder symptoms develop because of the social and psychological consequences of bulimia. Studies report the prevalence of lifetime affective disorder in patients with bulimia nervosa ranging from 24% to 88%. Anxiety disorders are also common in individuals with bulimia nervosa, particularly social phobia (see Mitchell et al., 1991 for a review).

It is not uncommon for bulimic patients to meet criteria for borderline, dependent, or histrionic personality disorders. Once again the relationship between the eating disorder and personality disorders is unclear. The personality disorder may predispose individuals to develop bulimia, or may be a consequence of the eating disturbance (see Mitchell et al. 1991, for a review).

The majority of bulimic women report significant life impairment. Interpersonal relationships suffer and social isolation often results either from fear of submitting to a binge episode in public, or in order to stay home and binge instead of engaging in social activities (Johnson & Connors, 1987).

Bulimics are usually ashamed of their behaviour and are therefore very secretive about their disorder. The symptoms are hard to recognize and their onset typically precede

treatment by 3 to 5 years. Frequent weight fluctuations are common, however, most bulimics are within a normal weight range. Despite normal weight, many bulimics show signs of starvation. Symptoms of starvation include loss of sleep, impaired concentration, indecisiveness, preoccupation with food, mood lability, irritability, anxiety, and depression. Physical manifestations may include hypothermia, edema, bradycardia, hypotension, and lanugo (see Haller, 1992 for a review).

Nearly 50% of bulimic patients demonstrate fluid or electrolyte abnormalities that can lead to cardiac arrhythmias, tiredness, and depression. Low potassium levels can lead to weakness in skeletal and smooth muscle, including decreased gastrointestinal motility, it may contribute to glucose intolerance, and also affects renal function. Other electrolyte abnormalities include hypomagnesemia, and hypocalcemia (see Mitchell et al., 1991 for a review).

Repeated vomiting can result in swelling of the parotid glands bilaterally, dental erosion, gingivitis, esophageal relaxation and subsequent reflex regurgitation, and in severe cases, esophageal tearing accompanied by bleeding or perforation. Constipation and impairment of colonic functioning can be caused by laxative abuse. Gastric dilation and perforation, gastrointestinal bleeding, gastric and duodenal ulcer and malabsorption syndromes are further

potential medical complications caused by bulimic behaviour (see Mitchell et al., 1991, & Haller, 1992 for reviews).

The course of bulimia nervosa tends to be episodic, with an overall trend toward improvement. It is a chronic disorder, with frequent relapses and even recovered patients continue to experience residual symptoms (see Haller, 1992 and Mitchell et al., 1991 for reviews). The probability of recovering (defined as 8 consecutive symptom-free weeks) has been reported to be 69% and the probability of relapse (defined as reversion to DSM-III-R criteria for two consecutive weeks) as 65%. The probability of recovering from the relapse episode is 50% (Herzog, Keller, Lavori, & Sacks, 1991).

Treatment approaches may combine psychotherapy, nutritional counselling, pharmacotherapy and medical care (Herzog, Keller, Lavori, & Sacks, 1991). The type of psychotherapy chosen depends on the favoured model of bulimia.

The cognitive-behavioural model of bulimia nervosa posits that societal pressure for thinness leads to dietary restraint with rigid food rules. This restraint results in extreme hunger, which leads to disinhibition manifested by binge eating. Cognitive-behavioural therapy has proven to be an effective treatment for bulimia nervosa (see Agras, 1991 for a review). The aim of treatment is to restore normal dietary intake in order to decrease binge eating and

consequently diminish purging. Cognitive elements such as rigid food attitudes and rules, distorted body image, and dysfunctional cognitive processes are challenged.

Environmental cues to binge, such as being alone with binge food, are attended to. A critical aspect of this therapy is self-monitoring of behaviour and the individual precipitants of binge episodes.

Response prevention, based on the theory that purging reinforces the binge/purge cycle, has also been demonstrated to be an effective method of treating bulimia (see Agras, 1991 for a review). In this form of treatment binge eating is elicited during the session and the patient then remains with the therapist until the urge to vomit has disappeared.

A third form of therapy that has been proven to be effective in reducing bulimic symptomatology is interpersonal therapy (see Agras, 1991 for a review). It is interesting that therapy that does not focus on eating patterns is effective in reducing bingeing and purging. The interpersonal model of bulimia nervosa proposes that interpersonal stress causes low self-esteem, leading to dysphoria. Food is used to cope with the negative feelings, resulting in binge eating. Interpersonal therapy focuses on interpersonal relationships and social impairment, both of which are sources of dissatisfaction for bulimics. The initial phase of therapy reviews the interpersonal context in which the eating disorder began. The focus then moves to

current relationships with an emphasis on expressing emotions. The goal is to teach the patient to cope interpersonally and not become overwhelmed by their emotions, to remain in control, and not resort to bingeing as a coping mechanism.

Biopsychosocial Model of Bulimia

The biopsychosocial model of bulimia lends itself to combined psychosocial and pharmacologic treatments. The exact etiology of bulimia has yet to be resolved but many researchers agree that it is a multidetermined disorder influenced by biological, psychological and sociological factors. The bulimic individual appears to suffer from affective instability and a low tolerance for frustration and anxiety that contribute to impulsive behaviour. Cognitive distortions influence her view of the world and people around her, and her place in society.

The individual with these psychological vulnerabilities experiences and responds to familial and social expectations. Research with families of bulimics suggest that they are more disorganized, more conflicted and have higher achievement orientation than families of normal controls (Johnson & Connors, 1987). The young woman who has grown up in this milieu may not have learned mechanisms for controlling her impulses nor dealing with her affective instability and yet is expected to excel. In today's society, physically attractive people are considered to

possess virtually every positive character trait and are believed to lead more successful and satisfying lives than unattractive people (Dion, Berscheid, & Walster, 1972). In order for a young woman to be considered physically attractive she must attain society's ideal female body image, which is slimmer than at any time since the 1930's (Davis & Crowles, 1991). Added to the concept of beauty is the concept of control. If a woman can control her weight, then she must be in control of her life and deserving of respect and approval.

Many adolescent females begin restricting their food intake in the pursuit of thinness which has become equivalent to the pursuit of self-control and self-esteem. However, for the psychologically vulnerable individual extreme thinking results in overvaluation of thinness and a rigid approach leads to severe dieting practices. This restriction contributes to affective instability accompanied by a preoccupation with food and cravings, and places her at greater risk for loss of control. Loss of control may take the form of binge eating, leading to feelings of failure, guilt, shame, and intense fear that she will gain weight. Purging behaviour by self-induced vomiting and/or laxative abuse emerges in an effort to reduce these negative feelings. Excessive purging may lead to malnutrition which contributes to binge eating, anxiety, depression, lack of concentration, mood swings, and lack of interest in

activities. The diet-binge-purge cycle may have biological as well as psychological consequences in that it may alter neurological pathways. And so the cycle is self-perpetuated, contributing to the chronic nature of the disorder (Goldbloom & Garfinkel, 1990).

Biological Contribution to Binge Eating

The DSM-III-R defines binge eating as "rapid consumption of a large amount of food in a discrete period of time". Bulimic patients report diminished satiety compared to controls following ingestion of high caloric carbohydrate rich foods (Chiodo & Latimer, 1986; Kissileff, 1986), and reduced satiety during a liquid meal compared to anorexics and controls (Halmi, 1988). Bulimics report having difficulty knowing when they are full at the end of a "normal meal". These results suggest a failure in the mechanism of satiety (Halmi, 1992), a mechanism believed to be mediated by the serotonergic pathways.

Dysregulation of serotonin function has also been connected with depression and impulsivity (Lopez-Ibor, 1988; Lopez-Ibor, 1992; Goldbloom & Garfinkel, 1990; Jimerson, Lesem, Hegg & Brewerton, 1990). Behavioural disinhibition and the desire to elevate mood may contribute to the impulse to binge eat in bulimic patients.

Role of Serotonin in the Control of Food Intake.

Experimental manipulations of serotonin metabolism via micro-lesions of the raphe nuclei, microinjections of

serotonin into the paraventricular nucleus of the hypothalamus, or administration of serotonergic agonists or antagonists result in alterations in feeding behaviour, food selection, and body weight (Morley & Blundell, 1988). The most consistent finding is that experimental manipulations that enhance serotonergic activity result in weight reductions and reduced food intake in the form of reduced meal size, rather than reduction of meal frequency. Some studies have shown that animals given dietary choice following administration of serotonin agonists selectively reduce carbohydrate intake but not protein intake. However, the idea that the level of serotonin synthesis and release can modulate nutrient selection is controversial (Lawton & Blundell, 1993).

Tryptophan, the substrate of serotonin, is not synthesized in the body and must be obtained through diet. Brain level of tryptophan is the rate-limiting step in the synthesis of serotonin. Tryptophan competes with other amino acids for entry to the brain. Therefore, tryptophan ratio to other amino acids, as well as total amount available, influences the availability of substrate. Increased availability of substrate should result in increased serotonin synthesis, serotonin levels within the nerve terminals, and release into synapses on firing.

Although tryptophan is an amino acid, ingestion of pure carbohydrate results in higher tryptophan/large neutral

amino acids (LNAA) ratios than ingestion of mixed or protein-rich food that elevate levels of all LNAAs. Carbohydrate intake results in the release of insulin which causes most amino acids in plasma to dissociate themselves from albumin and enter adipocytes, thus decreasing their plasma level. Tryptophan has a propensity to bind to albumin and the dissociation of other amino acid molecules increases albumin's capacity to bind to tryptophan. This loose bond retards tryptophan entry into tissues, increasing the tryptophan/LNAA ratio, but allows it to enter the brain, resulting in increased substrate availability. Since tryptophan comprises only about 1 to 1.5% of most proteins, ingestion of a protein-rich meal causes a decline in the plasma tryptophan ratio and therefore decreases tryptophan's transport into the brain and slows its conversion to serotonin (Wurtman & Wurtman, 1984). Brain serotonin synthesis is directly controlled by the proportion of carbohydrate to protein in meals and snacks (Wurtman, 1987).

The plasma elevation of tryptophan/LNAA ratio and subsequent increase in serotonin synthesis may provide a feedback mechanism in the regulation of carbohydrate intake (Wurtman, 1987). Tryptophan administration has been found to reduce carbohydrate selection and tryptophan depletion to decrease protein selection in humans (Young, Tourjman, Teff, Pihl, & Anderson, 1988). Animal research has shown that following two weeks of carbohydrate restriction, the

normally observed increase in serotonin synthesis in response to carbohydrate ingestion is reduced (Wurtman, 1987) and twice the amount of carbohydrate intake is required to activate serotonin satiety mechanisms (Wurtman, Moses and Wurtman, 1983). Thus, alteration in diet composition, (i.e. low carbohydrate diet) or calorie restriction such as fasting may result in compensatory changes in this feedback mechanism that contribute to cravings and bingeing on high carbohydrate foods (Wurtman, 1987). A history of dieting and bingeing may affect the brain's neurochemical response to foods and nutrients and establish a cycle of dietary dysregulation.

Evidence for Serotonin Involvement in Bulimia Nervosa.

Many bulimic patients experience affective instability, anxiety, seasonal affective disorder, obsessive compulsive tendencies and are prone to promiscuous and suicidal behaviour. Considerable evidence exists that serotonin is involved in each of these conditions, which suggests involvement in eating disorders themselves. Results of post-mortem studies of suicide victims suggest the existence of reduced presynaptic serotonin activity resulting in compensatory sensitivity of binding sites (Lopez-Ibor, 1992).

Response of bulimic patients in comparison to controls to a protein rich meal showed lower tryptophan/LNAA ratios and smaller plasma prolactin response. Lower

tryptophan/LNAA ratios coincided with longer binge episodes. It is possible that the lower ratio results in altered precursor availability and reduced levels of serotonin associated with impairment of the serotonin-mediated satiety response (Jimerson et al., 1990).

Investigation of the involvement of specific neurochemicals in psychopathology has often been conducted by measurement of the metabolism of the suspected neurochemical in populations possessing the psychopathology of interest. The measurement of serotonergic metabolism in vivo must be performed through indirect strategies. Researchers have used methods such as lumbar puncture and subsequent measurement of metabolites in the cerebrospinal fluid drawn. Measurement of concentration and activity of enzymes involved in serotonin metabolism and concentration and activity of receptors in platelet is also common. Another strategy involves evaluation of the changes in serotonergic activity induced by psychotropic drugs known to act on the serotonin system. A fourth strategy involves measurement of serotonergic probes such as the concentration in the peripheral blood of hormones such as prolactin, whose secretion is controlled by hypothalamic factors influenced by serotonin.

Kaye, Ebert, Gwirtsman. & Weiss (1984) showed the serotonin metabolite 5-hydroxyindole-acetic acid (5-HIAA) levels in the CSF to be substantially reduced in low-weight

anorexic patients. Following weight restoration these levels returned to normal range. However, when patients were subgrouped according to presence or absence of bulimic symptoms, patients with bulimic symptoms had significantly lower CSF accumulations of 5-HIAA after weight recovery than did non-bulimic patients.

In an attempt to determine whether bingeing behaviour may constitute an attempt to increase serotonin-mediated transmission, Kaye, Gwirtsman, Brewerton, George and Wurtman (1988) measured TRP/LNAA and plasma prolactin response during bingeing and vomiting. Patients were instructed to continue to binge and vomit until they had achieved a "desired effect". Six of the nine subjects experienced early increases in their plasma TRP/LNAA ratios, and these subjects stopped bingeing and vomiting after one to three episodes. The remaining three subjects did not experience increases in their TRP/LNAA ratios and continued to binge and vomit until they were asked to stop after the fourth episode. These subjects also reported that they still felt unsatisfied. Subjects who experienced increases in TRP/LNAA levels also showed greater increases in secretion of plasma prolactin than those ratios did not increase.

Kaye et al. (1988) suggest that while the question of whether bulimics binge and vomit in order to raise brain serotonin to compensate for an existing serotonergic disturbance cannot be definitively answered by their study,

the findings do support the hypothesis that brain serotonergic function may be related to bulimia nervosa.

In more recent studies bulimic patients as a group were found to have normal CSF 5-HIAA levels however, patients with a history of severe bulimic symptoms had metabolite levels lower than less symptomatic patients and lower than healthy controls (see Jimerson et al., 1990 for a review). These findings provide support for the theory that bulimia involves serotonin dysregulation and that this dysregulation accompanies severe symptomatology.

Weltzin, Fernstrom, McConaha, & Kaye (1994), proposed that selectively reducing serotonin should be a promising method of determining whether some of the symptoms of bulimia are associated with abnormal serotonin function. Following ingestion of an oral tryptophan-free amino acid mixture, including large neutral amino acids that compete with tryptophan for brain uptake, plasma TRP/LNAA ratios fell 9% in normal and 12% bulimic women. Bulimic women were found to be more anxious, overreactive, to show more body image distortion, greater indecision and exhibit a trend toward greater depression and fatigue after ingesting the TRP-deficient mixture than they did after consuming a TRP-containing control mixture. The normal women were also more depressed and overreactive following the TRP-deficient mixture than following the control mixture. Bulimic women, in comparison to control women, were more fatigued and

showed a tendency toward greater levels of anxiety and indecisiveness following the TRP-deficient mixture. The bulimic subjects also showed a trend toward reduction in anxiety after ingesting the TRP-containing mixture.

Measurement of serotonin uptake in platelet provides a possible model for serotonin re-uptake in the brain. Considerable evidence exists to suggest that serotonin may have its action terminated by being taken up into the presynaptic terminal (Cooper, Bloom, & Roth, 1991). Platelet serotonin uptake was found to be normal in anorexic patients but increased in patients with bulimia (Goldbloom, Hicks, & Garfinkel, 1990). If it can be assumed that this is a mirror for increased brain uptake, then it follows that in bulimics increased re-uptake could result in decreased synaptic serotonin availability. Goldbloom et al. (1990) suggest that the diminished serotonin activity at postsynaptic receptors at the hypothalamic level would result in decreased satiety signals, and possibly increased preference for carbohydrate.

Functional activity in hypothalamic serotonin pathways can be assessed through measurement of the increase in plasma prolactin level following administration of a serotonin agonist. Twenty-six bulimic anorectics, twenty of whom had been symptom free for three weeks, showed blunted plasma prolactin responses following administration of the post-synaptic serotonin receptor agonist m-

chlorophenylpiperazine (m-CPP) (Brewerton, Brandt, Lesem, Murphy, & Jimerson, 1990). Ten bulimic patients with concurrent major depression had lower peak levels of plasma prolactin levels than the 16 patients without depression, although this difference did not reach significance. Prolactin responses were negatively correlated with baseline cortisol and weekly binge frequency during the month prior to cessation of bingeing and purging. These results suggest a down-regulation of the serotonergic hypothalamic pathway. The blunted response could be a result of longterm downregulation of postsynaptic receptors as a result of bingeing and purging, or could reflect a premorbid state that contributed to the eating and affective disorders (Brewerton et al., 1990).

At the same time, bulimic patients' prolactin response to administration of L-tryptophan was not significantly lower than controls as a group, however, patients with concurrent major depression had significantly lower response than bulimics without depression and controls (Brewerton et al., 1990).

Brewerton et al. (1990) suggest that the different response by bulimics without depression to administration of m-CPP and L-tryptophan lies in the different mechanisms of action of the two agents. Prolactin response to L-Tryptophan involves both presynaptic and postsynaptic neurons, while response to m-CPP involves postsynaptic

neurons only. It may be that major depression involves predominantly a disruption of presynaptic serotonergic mechanisms while bulimia involves disturbance of postsynaptic sensitivity. Post-synaptic subsensitivity may be countered by increased presynaptic output in the non-depressed bulimic. Therefore, prolactin response to L-Tryptophan would be normal and platelet re-uptake would be increased, while response to m-CPP would be reduced. The adaptive increase in serotonin output may fail during the development of major depression (Brewerton et al., 1990).

However, as previously reported, bulimic patients who binge twice a day had CSF 5-HIAA levels lower than controls and bulimics who binged less frequently. The lower metabolite measure suggesting decreased presynaptic neuronal serotonin synthesis is in conflict with the hypothesis of increased presynaptic output, as is the absence of compensatory up-regulation of post-synaptic response. Dieting in healthy volunteers has been shown to decrease presynaptic release of serotonin, accompanied by an up-regulation of postsynaptic serotonergic responses mediating prolactin secretion. Jimerson et al. (1990) propose that postsynaptic compensation is not observed in bulimic patients because of the intermittent surges in serotonin synthesis following binge episodes.

Pharmacological Treatment of Bulimia

Evidence for involvement of a putative neurochemical in

psychological disorders can also be provided by the relief of symptoms by drugs known to act on that neurochemical system. Serotonergic transmission can be enhanced by drugs that block serotonin reuptake, enhance serotonin release, or directly activate receptors. Patients presenting with bulimia often have a co-diagnosis of depression, the treatment of which opened the door to research showing that antidepressant medication in the form of both the tricyclics and the monoamine oxidase inhibitors (MAOIs) are effective in reducing bulimic symptoms (Walsh & Devlin, 1992).

In his description of the syndrome of bulimia nervosa, Russell (1979) pointed out that next to severe concerns with eating and weight, depressive symptoms were the most characteristic feature of bulimic patients' mental state. However, he was not of the opinion that bulimia nervosa could be accounted for by a primary depressive illness, and while he advised pharmacotherapy in treating severe depressive symptoms, he did not believe antidepressants would influence the eating disorder. Sabine, Yonace, Farrington, Barratt and Wakeling (1983) decided to test Russell's beliefs by conducting a controlled trial of mianserin in bulimic patients.

Fifty mildly depressed bulimic patients were randomly allocated to receive either placebo or 30 mg mianserin (increased to 60 mg after one week) daily. Thirty-six patients completed the eight-week trial. Each subject kept

a daily record of whether she had binged or not and completed the Multiple Affect Adjective Check List (MAACL). Depression was assessed every two weeks with the Hamilton Rating Scale for Depression (HAM-D). Binge frequency did not change throughout the eight-week period for either group but depression scores fell for both groups, and there were no significant differences between groups. When Sabine et al. (1983) compared the mood scores from the (MAACL) on binge days to binge-free days, they found that mood scores were higher on the binge days. These authors conclude that bulimia is not a manifestation of an underlying affective disorder, but that mood changes accompany bulimic behaviour.

Growing evidence of phenomenological similarities between patients with bulimia and patients with major depression prompted Pope, James, Hudson, Jonas and Yurgulund-Todd (1983) to try antidepressant drugs in the treatment of bulimic patients. Favourable responses led them to conduct a double-blind, placebo-controlled study of imipramine treatment of bulimia. Twenty-two patients were randomly assigned to imipramine hydrochloride (50 mg) or inert placebo groups. Subjects were instructed to begin taking one tablet at bedtime, and to increase the dosage by one capsule every other day to a total of four capsules per day. Three subjects withdrew from the study in the first three weeks, two because of side effects. At two-week intervals subjects were administered the HAM-D and reported binge

frequency over the last two weeks. At the end of six weeks subjects in the placebo group were offered a supervised trial of imipramine and subjects in the active drug group were given the option of continuing treatment with imipramine or changing to another antidepressant.

Binge frequency in the active drug group decreased by 70% compared to no change in the placebo group. Depression scores for the imipramine group also declined significantly more than for the placebo group and decline was significantly correlated with binge frequency reduction. Follow-up data on the 20 of the 22 subjects who received a complete trial of imipramine and/or another antidepressant medication subsequent to the drug trial revealed moderate to marked improvement in 90%.

These authors interpret their results as proof of a direct relationship between antidepressant effects and antibulimic effects based on the correlation between depression scores and binge reduction, response to numerous antidepressants employed after the blind trial (desipramine, nortriptyline, tranylcypromine, and trazodone), and the timing of the antibulimic effect (about 2-4 weeks) as would be expected for antidepressive response. Pope et al. (1983) further suggest that their results augment the phenomenologic evidence that bulimia may represent a form of affective disorder. It should be noted that subjects were not assessed after one week drug therapy and that the

antibulimic effect may have commenced prior to the antidepressive effect suggesting concomitant yet unrelated drug effect.

Mitchell and Groat (1984), further investigated the treatment of bulimia with antidepressant medication. In a double-blind, placebo-controlled trial of amitriptyline hydrochloride 32 bulimic subjects completed an eating behaviour inventory daily, and were seen weekly during the study. Depression was assessed by the HAM-D and the Zung. Following a two-week baseline period subjects were stratified as either depressed (HAM-D scores greater or equal to 20) or nondepressed (HAM-D scores less than 20) and subsequently randomized to active or placebo groups. Subjects began taking one pill (50 mg amitriptyline or placebo) at bedtime, this dosage to be increased to three pills by the end of the week. In addition to drug treatment, subjects received minimal behavioural advice such as encouragement to not worry about weight, the importance of regular meals, and positive feedback for symptom reduction.

Following eight weeks of drug therapy, subjects in the amitriptyline group had reduced their weekly binge frequency by 76.7% and the placebo group's binge frequency was reduced by 51.8%, a non-significant difference. Subjects receiving active antidepressant medication were significantly less depressed than the control subjects when assessed on the

HAM-D. Depressed subjects in the active drug group improved to the level of the non-depressed group. Depressed subjects reduced bingeing behaviour significantly less than the non-depressed subjects. Change in eating dysfunction was significantly correlated with changes in depression for the total sample and the depressed sample.

While the difference between the amitriptyline and placebo groups' decrease in binge frequency was non-significant, the differences favoured the active drug. Mitchell et al. (1984) suggest that the improvement in the placebo group was due to the minimal behavioural intervention and that this intervention was less effective in the depressed subjects. They conclude that antidepressant therapy can be quite beneficial, at least in terms of mood, in patients with bulimia. They also suggest that their results contribute to the literature suggesting a possible relationship between bulimia and affective disorders and raise the possibility that changes in depression might be accompanied by changes in eating dysfunction. However, these results could also be interpreted as decrease in depressive symptoms accompanying decrease in binge frequency, as well as providing evidence that antidepressant medication effectively reduces bulimic behaviour in the absence of depression.

Hughes, Wells, Cunningham, and Ilstrup (1986) performed a double-blind, controlled partial-crossover trial of

desipramine versus placebo with 22 subjects who met DSM-III criteria for bulimia but not Research Diagnostic Criteria for major depressive disorder. Subjects in the active drug group began with one 50-mg tablet taken at night. This dose was increased by 50 mg every three days until a target dose of 200 mg nightly was attained. Binge frequency was obtained by weekly self-reports and depression was measured on the Zung self-rated depression scale. Subjects in the desipramine group decreased their weekly binge frequency by 91% by week six and subjects in the placebo group increased their frequency by 19%. Depression scores for the desipramine group fell 10 points and the placebo group's scores fell 1.3 points. Subjects initially taking placebo crossed over to desipramine and subsequently decreased binge frequency by 83.7%, and depression scores fell 5 points.

Only six of the 20 patients available for testing had serum desipramine levels within the therapeutic range for depression. Ten subjects were subtherapeutic and four of these subjects had attained complete remission. Doses were increased for the other six and complete remission was then achieved for four of these six subjects. Four subjects were supratherapeutic and dosage was reduced in order to relieve side effects. No significant change in symptom severity resulted. Hughes et al. (1986) interpret the success of desipramine in a non-depressed population as evidence that the effect of the drug is due to antibulimic properties and

recommend further research into the therapeutic desipramine level for bulimia.

Walsh, Stewart, Roose, Gladis and Glassman (1988) conducted a ten-week treatment study with the monoamine oxidase inhibitor, phenelzine. Eighty-two bulimic patients entered a two-week single-blind placebo phase. During this wash-out phase 20 patients were dropped from the study because of non-compliance to a tyramine-free diet, missed scheduled appointments, or placebo response. Sixty-two patients who continued to binge at least three times weekly were randomly assigned to receive either phenelzine or an inert placebo. Dosage was gradually raised to four pills per day (60 mg) over two weeks. Twelve subjects were not included in analysis because they were dropped from the study for non-compliance to drug administration for at least two weeks. Commencing week 4, non-responders' daily dosage was increased one pill each week to a maximum of six pills by the end of week six. Forty-nine subjects remained in the study for at least six weeks. During the last two weeks six placebo-treated patients dropped out because of frustration with lack of results and five phenelzine-treated patients left the study citing side-effects as their reason.

Binge frequency was recorded in a diary and this information was collected weekly along with HAM-D scores. The phenelzine group's binge frequency reduction was significantly greater, 64% vs 5%, than the placebo group's.

The mean total scores on the HAM-D were not significantly different for the groups at the end of ten weeks, however, when status at termination with that at randomization were compared the phenelzine-treated group showed a significantly greater reduction in depressive symptoms than the placebo group.

Twenty-eight of the 50 completers had been classified as depressed at randomization. Phenelzine-treated depressed subjects responded significantly better than placebo-treated subjects in terms of bingeing and depression than placebo-treated subjects. Non-depressed phenelzine-treated subjects showed a significantly greater decline in binge frequency than non-depressed placebo-treated subjects. Statistical analysis revealed that while patients classified as depressed did significantly worse than those classified as not depressed, the effect of phenelzine on bulimic symptoms was not related to the presence or absence of depression.

Based on the results of these and previously reported results of this study (Walsh, Stewart, Roose, Gladis & Glassman, 1984; Walsh et al., 1985) these authors conclude that phenelzine is superior to placebo in the treatment of normal weight bulimic women, but that side effects pose a major problem for its use. They reject the hypothesis that phenelzine works in bulimia through its antidepressant effect, and suggest that it may be mediated by the action of this drug in the relief of feelings of anxiety and tension,

feelings that typically precede, and possibly stimulate a binge episode or via a direct effect on neurobiological systems that regulate the control of eating behaviour.

In an attempt to further explore effective pharmacological treatment of bulimia nervosa while excluding all other therapeutic intervention Agras, Dorian, Kirkley, Arnow, and Backman (1987) conducted a 16-week trial of imipramine hydrochloride with controlled therapist/patient interaction. Twenty-two bulimic patients entered the study. Subjects were seen by a physician weekly for the first 4 weeks and thereafter at 2-week intervals. A standard interview protocol was followed wherein reports of binge and purge frequency over the last week were obtained and medical information exchanged. No advice or encouragement concerning bulimic behaviour was extended. Subjects were required to keep daily diaries of binge and purge frequency only for the week during baseline, during the sixth and sixteenth study weeks in order to minimize the effect of self-monitoring. The BDI and the Eating Attitudes Test (EAT) were administered at the same intervals.

Patients receiving imipramine decreased their purging by 44% by 6 weeks and by 72% by 16 weeks, in comparison to decreases of 12% and 35% in the placebo group. The changes in binge frequency paralleled those for purging. These improvements were significantly different, as was improvement in depression. The active drug group reduced

their BDI scores by 46% at 6 weeks and 51% at 16 weeks compared to 24% and 25% reductions in the placebo group. Improvement in bulimic behaviour was not correlated with decrease in depression.

Agras et al. (1987) investigated age, duration of bulimia, baseline scores on the EAT, lowest reported body mass index (BMI), and reduction in purging as potential predictors of outcome. Only the lowest reported BMI since the onset of bulimia was significantly associated with reduction of purge frequency. Subjects with lower BMIs (possibly a measure of intensity of dietary restriction) did less well than those with higher BMIs.

These authors interpret their results as confirming those of Pope et al. (1983) that imipramine is more effective than placebo in the treatment of bulimia but since the relationship between behavioral improvement and reduction in depression was not replicated, question their conclusion that bulimia may represent a form of affective disorder. Agras et al. (1987) suggest that an alternative explanation is that depression improves as a consequence of reduction in binge eating and purging.

Barlow, Blouin, Blouin, and Perez (1988) selected the antidepressant desipramine to continue the investigation of drug treatment of bulimia. Desipramine is a relatively specific norepinephrine re-uptake inhibitor and animal research has demonstrated an anorexiatic activity of

norepinephrine.

Forty-seven depressed and non-depressed bulimic patients were enrolled in this double-blind crossover study. Patients were randomly assigned to drug or placebo for the first six weeks, followed by a three-week washout period for all subjects, and then six weeks of the reverse condition. Dosage was increased from 50 mg to 150 mg over the first week. Subjects reported average weekly binge frequency after the first week and then bi-weekly when they completed the Hopkins 90-item Symptom Checklist (SCL-90) and the Profile of Mood States (POMS), which provide two independent measures of depression. Twenty-four subjects completed the study. Eight subjects dropped out because of side-effects and fifteen left the study for personal reasons such as time constraints.

Subjects receiving desipramine significantly reduced bingeing and purging when compared to those receiving placebo as early as week one. There were no significant changes on the depression scales which may have been the result of low dosage. Only three of the twelve subjects tested had blood levels of desipramine within therapeutic range for treatment of depression. The reduction in bulimic behaviour in the absence of effect on depression suggests that the effects are mediated through different mechanisms and Barlow et al. (1988) hypothesize that the direct anorexiatic effects of norepinephrine are responsible for desipramine's antibulimic

effect.

Encouraged by promising studies with a variety of antidepressants but concerned with the proportion of bulimic patients that appear to experience serious side effects, Horne et al. (1988) were prompted to conduct a study of the efficacy of bupropion in reducing bulimic symptoms. This unique antidepressant was believed to display fewer anticholinergic, sedative, and hypotensive side effects than tricyclic antidepressants and monoamine oxidase inhibitors.

Eighty-two bulimic patients who did not meet DSM-III criteria for current major depression were enlisted in a placebo-controlled, double-blind eight-week study. Following a one-week placebo washout period one placebo responder was dropped from the study and the remaining subjects were randomized in a 2:1 ratio to active and placebo groups respectively. Dosage was increased from 225 mg/day to 450 mg/day over the first 10 days. Subjects kept a daily diary of binge eating and purging and were evaluated on the HAM-D at Weeks 0, 1, 2, 4, 6 and 8.

Early termination of the study because of four bupropion subjects experiencing grand mal seizures reduced the number of completers to 37 bupropion and 12 placebo subjects. Binge frequency of the bupropion group was reduced by 39.4% in 1 week and 67.0% by 8 weeks. This reduction was significantly greater than the placebo groups' 1.9% decrease from baseline. As would be expected in a non-

depressed group HAM-D scores showed little change.

Horne et al. (1988) suggest that the finding that bupropion, a chemically different drug but similar in its efficacy in treating depression, is equally effective as the tricyclics and monoamine oxidase inhibitors in reducing bulimic symptoms lends support for the speculation that these drugs ameliorate both bulimic and depressive symptoms through similar mechanisms. However, they do not rule out the possibility that bupropion may have an unknown anorexigenic effect since reduction in bingeing was evident after only one week, sooner than an antidepressant effect would be expected.

In 1987 the DSM-III-R proposed narrower criteria for the diagnosis of bulimia nervosa, specifically the presence of "persistent overconcern with body shape and weight", thus eliminating patients that might be suffering from hyperphagic depression rather than bulimia nervosa. Pope, Keck, McElroy, and Hudson (1989) felt that the results of earlier antidepressant studies of bulimia using the broader criteria must be viewed with caution. At the same time, they postulated that additional antidepressant agents should be explored because of the non-response of some subjects in each study and the adverse side effects experienced. In order to address these concerns, Pope et al. (1989) conducted a placebo-controlled double-blind study of trazodone in the treatment of patients meeting the new

criteria for bulimia nervosa.

Fifty-six patients entered a 2-week placebo washout period. Ten subjects were eliminated and the remaining 46 were randomized to trazodone or placebo. Subjects received 50-mg tablets and were instructed to raise the dose by one tablet every second day to a maximum of eight tablets (trazodone 400 mg). Bulimic behaviour was recorded in daily diaries and reported bi-weekly, at which time the HAM-D was administered. Forty-two subjects completed at least 4 weeks of treatment and 37 remained until the 6-week termination evaluation. No subjects dropped out citing exclusively side-effect as the reason.

The trazodone group reported a 31% reduction in binge eating by termination compared to the placebo groups' 21% increase. This reduction was a significant difference from baseline as well as being significantly different from the placebo group's increase. There were no differences between groups on the HAM-D probably reflecting the fact that many subjects exhibited only modest levels of depression to begin with.

Pope et al. (1989) speculate that the mechanism of action of trazodone may lie in its serotonergic agonist properties, but since desipramine, which has virtually no effect on serotonin, has been shown to be effective in reducing bulimic symptoms they limit their conclusion to the observation that a range of drugs effective for depression

appear to be effective for bulimia nervosa.

Since most studies of antidepressants in bulimia had been with tricyclics and only one monoamine oxidase inhibitor had been tested, Kennedy et al. (1988) chose to conduct a 13-week, double-blind, placebo-controlled crossover trial of the MAOI isocarboxazid. Treatment periods of six weeks were divided by a 1-week washout period. Patients completed a daily self-report questionnaire on general food consumption, bingeing and vomiting and were seen at intervals at which time the HAM-D was administered. Dosage was gradually increased from 10 mg to 60 mg by the end of four weeks. Of the 29 bulimic patients who entered the study, 24 completed the first six-week phase and 18 completed both phases. Only one drop-out cited side effects as the reason for terminating participation, however, over 50% of subjects reported adverse side effects.

When the scores from the two phases for each of the 18 patients were compared, there was a significant reduction in bingeing and vomiting frequency during the isocarboxazid treatment. After six weeks of isocarboxazid treatment scores on the HAM-D were significantly lower. When the drug vs placebo groups in the first phase (24 subjects) were compared the isocarboxazid group reported significantly lower vomiting frequency, but the reduction in binge eating was not significant. When patients were divided into two

groups based on more or less than 50% improvement there was a significant drug effect for both bingeing and vomiting.

In interpreting their results Kennedy et al. (1988) address possible reasons for the effectiveness of isocarboxazid therapy. As an antidepressant it might have preferentially treated depressed subjects, but there was no difference in response between depressed and non-depressed subjects in this study. A second possibility is that the drug relieves bulimic symptoms through its anxiolytic effect. The possibility that the drug is acting directly on feeding behaviour through its effect on noradrenergic and serotonergic systems is the third possibility. Evidence for serotonin abnormalities in bulimia and the co-existence of depression and impulse-related problems in bulimic patients are presented in support of this third hypothesis.

The foregoing studies, conducted by individual laboratories, necessarily involved relatively small samples. Small samples limit the statistical power in the assessment of the drug effect on primary symptomatology as well as the assessment of possible predictors of drug response. Added to this, a sizeable number of patients remained symptomatic following trials either because of lack of medication efficacy or difficulty in tolerating adequate dosages of previously tried pharmacotherapeutic agents. For these reasons a multi-centre, placebo-controlled, double-blind 8-week trial of the novel antidepressant, fluoxetine

hydrochloride was conducted (FBNC Study Group, 1992). This drug is a specific inhibitor of serotonin uptake in the brain. Following an initial 1-week washout period 387 of the original 442 patients enrolled in the study were randomly assigned to receive placebo, 20 mg/day or 60 mg/day of fluoxetine. Patients recorded bingeing and purging frequency in daily diaries and were seen weekly during the study. The HAM-D was administered weekly.

One hundred and seventeen patients discontinued participation in the study, but only 5% of these dropouts cited side effects as the reason. Forty-eight dropouts were in the placebo group, 30 in the 20 mg/day group, and 39 in the 60 mg/day group.

The 60 mg/day group's reduction of bulimic symptomatology scores was significantly greater than the placebo groups' at weeks one through seven. Reduction in vomiting frequency but not binge frequency was significantly different for these groups at week 8. Depression scores on the HAM-D were also significantly reduced by week 8. Fluoxetine at 20 mg/day was intermediate in its effect: superior to placebo for vomiting and inferior to 60 mg/day for both vomiting and bingeing. At the end of the 8-week trial groups receiving 60 mg/day, 20 mg/day, and placebo had median reductions of 56%, 29%, and 5% respectively in vomiting episodes per week, and median reductions of 67%, 45%, and 33%, respectively, in binge eating. Small, though

statistically significant correlations were found between blood level concentration of fluoxetine and improvement in bulimic symptoms. Body mass index, degree of carbohydrate craving, severity of depression, and overall severity of the eating disorder as determined by the EAT total score were examined as possible predictors of response. The only significant finding was that BMI predicted binge-eating response: heavier patients had higher response rates in each treatment group.

The FBNC Study Group (1992) suggest that fluoxetine offers some advantages over previously tried antidepressants because of the modest incidence of side effects and the low discontinuation rate as a result of inability to tolerate adequate dosage. Once again, the mechanism by which this drug works is uncertain. Severity of depression at baseline was not significantly associated with response and these researchers hypothesize that the mechanism of action of fluoxetine may lie in its serotonergic enhancement of satiety and inhibition of carbohydrate craving. However, they point out that other antidepressants with negligible effects on serotonin neurotransmission have also proven effective in bulimic patients.

In order to further investigate the efficacy of monoamine oxidase inhibitors in the treatment of bulimia nervosa, Kennedy et al. (1993) selected brofaromine, a selective and reversible inhibitor of monoamine oxidase-A

with safer adverse reaction profile than previously employed MAOIs. Thirty-eight bulimic patients enrolled in an 8-week placebo-controlled trial. Two subjects were eliminated following a 1-week placebo washout period. The remaining 36 patients were randomly assigned to receive placebo or 25-mg capsules of brofaromine. Capsules were to be taken twice daily and dosage was to be increased on days 4, 7, 11, 15 and 19 to a total of 200 mg of brofaromine provided that side effects at this dose could be tolerated. Subjects recorded frequency of binge eating, vomiting and consumption of non-binge meals in a daily diary and reported these data when they were seen bi-weekly. Depression was assessed with the HAM-D at baseline and termination. Four subjects dropped out of the study after a minimum of 4 weeks, two of whom were experiencing intolerable side effects (nausea) from the active drug.

The brofaromine group reported significantly fewer vomiting episodes than the placebo group, but the difference in binge frequency was non-significant. At the end of the trial, 44% of the brofaromine group and 20% of the placebo group abstained from vomiting and 19% of the brofaromine group and 13% of the placebo group abstained from binge eating. There were no differences between groups in depression ratings.

Although initial conclusion from this study is that brofaromine was not superior to placebo in reducing binge

eating, Kennedy et al. (1993) point out that the lack of statistical significance may have been the result of procedural shortcomings. They point out that the high response of the placebo group may warrant a longer washout period, and that nondrug aspects of the trial such as the possible benefits of repeated symptom assessments may have a substantial influence. Drug effect may have been concealed by a type II error because of the small sample size. In addition, although plasma brofaromine measures indicated that patients had detectable levels of the drug in blood, these authors suggest that they may have selected an inadequate dose of brofaromine.

It has been suggested that reduction in bulimic symptoms in response to antidepressant medication is a direct result of alleviation of depression (Pope et al., 1983). However, there are several lines of evidence that suggest that the effect is independent of depression. The presence or absence of depression does not predict degree of improvement in bulimic symptoms (Walsh et al., 1988, Kennedy et al., 1988, Pope et al., 1988, Walsh & Devlin, 1992). In fact, antidepressants are equally effective in reducing symptomatology in non-depressed patients (Hughes et al. 1986; Blouin et al., 1988; Horne et al. 1988). Mitchell and Groat (1984) found that depressed patients improved less when treated with amitriptyline than nondepressed subjects. Added to this, reduction in bulimic symptoms are observed

immediately while there is typically a two-week delay for the therapeutic effect of antidepressant drugs on depression.

Attitudinal change in response to pharmacotherapy.

Diagnostic criteria for bulimia nervosa include the presence of disturbed attitudes toward shape and weight and a feeling of lack of control over eating. Eleven of the studies of pharmacological treatment of bulimia previously reviewed in this paper addressed the cognitive effects of drug therapy.

Pope et al. (1983) had subjects rate themselves on a 5-point scale on three subjective indices - intensity of binges, preoccupation with food, and self-control with relation to food. When compared with placebo, imipramine treatment was associated with a significant decrease in the first two measures and a nearly significant decrease in self-control with relation to food. Walsh et al. (1985, 1988) measured cognitive symptoms with the EAT, and found that the phenelzine-treated patients had significantly lower scores than the placebo group. Blouin et al. (1988), employing the Eating Disorder Inventory (EDI), reported improvement in the Bulimia subscale in patients after receiving fenfluramine or desipramine, but not following placebo administration. Patients treated with isocarboxazid reported a reduction in pathological eating attitudes according the EAT (Kennedy et al., 1988). Fluoxetine was effective in reducing Bulimia scores on the EDI, as well as

scores on the Drive for Thinness and Body Dissatisfaction scales when compared to placebo (Goldbloom & Olmsted, 1993). Both the placebo group and patients receiving mianserin demonstrated significant improvement on EAT scores (Sabine et al., (1983).

Subjects receiving trazodone improved slightly on subscales on the EDI (Pope et al., 1989) but this improvement did not reach significance. Barlow et al. (1988) reported similar results with desipramine. Subjects in the imipramine group in the study by Agras et al. (1987) significantly improved in their eating attitudes by week 16 as measured by the EAT, but the difference between groups was not significant. Kennedy et al. (1993) found no differences on the EDI between placebo and brofaromine groups.

Summary of antidepressant treatment of bulimia. In summary, antidepressants of differing structures and pharmacologic properties have been found to be effective in the treatment of bulimia. It has been suggested that stimulation of the serotonergic pathway by these drugs underlies their effect on bulimia, but since many of these drugs are non-specific to this neurochemical, the mechanism behind the reduction in bulimic symptoms is difficult to determine. In addition, while involvement of serotonergic transmission may be the key, it may be that the mechanism of action of the anti-depressant drugs on bulimia and

depression may be very different. Platelet serotonin uptake has been demonstrated to be increased in patients with bulimia and decreased in patients with depression confirming a serotonergic dysregulation in both disorders, but suggesting different abnormalities.

Treatment of bulimia with fenfluramine. Fenfluramine is an indirect serotonin agonist. It enhances serotonergic transmission by blocking serotonin reuptake and enhancing serotonin release from nerve terminals (Garattini, Mennini, & Samanin, 1987; Garattini, Mennini & Samanin, 1989). The combined inhibition of uptake and augmented serotonin release results in increased neurotransmitter availability at post-synaptic receptors which should enhance serotonergic transmission (Garattini, Mennini & Samanin, 1989).

Heightened feelings of satiety after ingestion of food has been demonstrated as quickly as hours after administration of fenfluramine (Robinson, Checkley & Russell, 1985). Fifteen outpatients of an eating disorders clinic were randomly assigned either 60 mg of fenfluramine hydrochloride or placebo in a double blind condition. Two hours later blood samples were taken for serum fenfluramine estimation. Patients were left alone with previously chosen foods and asked to eat some, and as much as they wished within 30 minutes. The food was weighed before and after the test period and the caloric content of the food eaten was calculated. Subjects were asked to characterize the

eating experience and to complete 100 mm visual analogue scales every 30 minutes on not at all hungry to extremely hungry, not at all full to extremely full, and no urge to eat to extreme urge to eat. Subjects were asked to record their bulimic episodes and food consumed over the next five days. The same procedure was repeated one week later in order to make placebo/active drug comparisons. A normal control group was tested under the same conditions as the patients, but only given placebo.

The number of calories consumed after fenfluramine administration was significantly less than after placebo and there was a negative correlation between blood levels of drug and calories eaten. Patients consumed more calories after receiving placebo than did control subjects. Four patients characterized their eating after placebo as binges, and two felt they were 'near binges'. No patients considered their eating episode after fenfluramine a binge. After receiving placebo, patients' hunger ratings fell less after eating than controls' hunger ratings. Patients' hunger ratings fell more with fenfluramine than with placebo. Patients, having received placebo increased their ratings of 'urge to eat' after eating, while their ratings fell with fenfluramine. Ratings of fullness rose after all three conditions. Bulimic episodes in the 20 hours following the ward test did not differ between placebo and fenfluramine conditions.

Fenfluramine reduced the quantity of food consumed under laboratory conditions, increased feelings of satiety and reduced the urge to eat following food consumption, and suppressed bulimic episodes. Robinson et al. (1985) propose that the reduction in bulimic episodes may result because fenfluramine reduces food intake, therefore preventing a "threshold" of consumption that may be the trigger point of a binge. Alternatively suppression of bulimia by this drug may suggest that there is a disorder of neural control of eating in this disorder that can be modified by drugs. And finally, the abnormal increase in the urge to eat after a meal was reversed by fenfluramine, suggesting that it may act to facilitate mechanisms underlying satiety, thus suppressing bulimia.

To extend the results of Robinson et al. (1985) on the satiety-inducing effects of fenfluramine to determine whether it could be a clinically effective treatment of bulimia, and to investigate the relationship between bulimic and depressive symptoms, Blouin et al. (1988) investigated the effects of dl-fenfluramine and the antidepressant drug, desipramine in a population of bulimics. Desipramine has been reported to have anti-bulimic properties (Hughes et al., 1986). In a placebo-controlled, crossover design Blouin et al. (1988) monitored bulimic and depressive symptomatology in a 15-week study with 36 normal weight bulimic patients. Half the subjects in each group received

either 60 mg of dl-fenfluramine or 150 mg of desipramine for the first six weeks and half received placebo. After a 3-week wash-out period subjects crossed over for the next six weeks. All subjects completed the National Institute of Mental Health Diagnostic Interview Schedule, the EDI, the bulimia section of the Diagnostic Interview for Children and Adolescents (DICA), the POMS, the Moos Family Environment Scale, and the SCL-90.

To monitor bulimic symptomatology and psychopathology the EDI, the SCL-90, and the POMS were administered at weeks 0, 2, 4, 6, 9, 11, 13, and 15 and self-report recall of average weekly binge and purge frequency was obtained. Fourteen subjects dropped out of the study over the 15-week period, but only four subjects cited side-effects as the reason for discontinuing.

Fenfluramine significantly reduced daily vomiting from the first day to the end of the 6-week trial. Total bulimic symptomatology comprising of binge, vomit and other forms of purging was significantly reduced from week one to week six. Significant reduction in the psychological urge to engage in bulimic behaviour as measured by the bulimia scale of the EDI appeared in week four. Findings for desipramine were similar, but reduction in the psychological urge did not appear until week six. The authors suggest that this difference was related to the gradual increment in dosage of desipramine over a 1-week period in contrast to immediate

target dosage of fenfluramine. Responders were identified as subjects who exhibited reduced symptomatology at, or greater than, two placebo standard deviation units. Six of the 12 fenfluramine subjects exceeded, and two were close to exceeding 95% confidence limits. Two subjects from the desipramine group met this criteria.

Depression, measured on the SCL-90, was significantly reduced from week 2 to week 6 in the both the fenfluramine and desipramine groups. The depression scale of the POMS yielded similar results.

The antibulimic aspect of fenfluramine is believed to derive from satiety-promoting properties of enhancement of serotonergic transmission in the ventromedial hypothalamus. Desipramine is presumed to enhance noradrenergic transmission, and like amphetamine, may reduce hunger, thus having an effect on bulimic symptoms (Blouin et al., 1988).

In order to explore the effectiveness of dexfenfluramine (a more potent isomer of dl-fenfluramine) in reducing bulimic episodes, and to assess its adverse effects on mood, dietary intake, and weight, Russell et al. (1988) conducted a double-blind, placebo-controlled trial of 42 bulimic patients. Patients were randomly assigned to placebo or active drug groups. The trial was designed to last 12 weeks with the Clinical Psychopathology Rating Scale (CPRS), BDI, and the EAT completed on recruitment and at 2-week intervals during the trial. Weight and adverse

reactions were monitored and one hour of educational and supportive psychotherapy was conducted at the same intervals. Subjects kept a daily diary of overeating, food restraint, self-induced vomiting and purging. Patients in the active drug group received one 15-mg capsule daily, about two hours before the evening meal for the first two weeks and two capsules daily (one before breakfast and one before dinner) thereafter.

Dexfenfluramine appeared to significantly reduce overeating episodes when all 42 patients were considered, however, this finding is confounded by the fact that 17 patients dropped out of the trial, at about 6 weeks on average. When the results of completers versus non-completers are separated the effect is seen only in the group of non-completers. Similar findings were obtained in the reduced frequency of self-induced vomiting. No significant differences were found in depression ratings or eating attitude measures.

Nine non-completers had been allocated to the placebo group. Their symptoms worsened in the first six weeks, which may account for their decision to cease participating in the study. On the other hand, non-completers in the dexfenfluramine group showed a significant decrease in the number of binge and purge episodes. In an effort to explain the reasons for dropout, Russell et al. (1988), explored differences between unwanted effects, weight gain,

depression scores, EAT scores, allocation to active drug/placebo conditions, and previous history of anorexia nervosa between completers and non-completers. The fall in depression scores and EAT scores was significantly less at six weeks for non-completers and although difference in weight gain was non-significant, non-completers did gain more weight. These authors suggest that the persistence of psychological symptoms and poor tolerance of weight gain may have been instrumental in the decision to leave the trial.

Despite the complication surrounding the high drop-out rate in this study, Russell et al. (1988) conclude that the results of this study provide evidence that dexfenfluramine is superior to placebo in reducing bulimic symptomatology. However, they caution about the generalizability of these results because the initial randomization may have been upset by the high proportion of patients leaving the study.

In a more recent study, Fahy, Eisler and Russell (1993) investigated the effectiveness of dexfenfluramine in conjunction with psychological intervention in the treatment of bulimic patients. Forty-three patients were randomly assigned active drug or placebo in a double-blind eight-week trial of pharmacotherapy and psychotherapy. Dosage of dexfenfluramine began at 15 mg once daily and was incremented weekly to three times daily. Cognitive-behavioural therapy was conducted weekly. Patients kept a food diary that included information on bingeing and purging,

and completed the EAT and the Bulimic Investigatory Test, Edinburgh (BITE) on alternate weeks. The Montgomery-Asberg Depression Rating Scale (MADRS) was administered at four-weekly intervals. Patients were asked to continue their diaries for eight weeks after drug therapy and were interviewed and completed the EAT, BITE and MADRS at the end of this period. Four patients in the placebo group dropped out before the fourth week.

Over the eight-week treatment period, and at the 8-week follow-up, there was a significant reduction in bulimic symptomatology in both groups, and no difference between groups. Measures of psychopathology on the BITE and EAT tests were also significantly reduced over the 8-week period. The BITE symptom scores showed a significantly better course for the dexfenfluramine group. There was no significant group difference in MADRS scores, and the authors do not report whether depression, as measured by this test, was significantly reduced in both groups over the trial or not. There was no difference in effectiveness of drug or placebo for patients who obtained initially high scores of depression nor for patients with personality disorders. Although the placebo group showed a tendency to gain weight and the dexfenfluramine group lost weight, the changes between groups were not significant. Thirty-seven patients completed the BITE and the EAT 1 year after the start of treatment. No significant differences were found

between the active drug and placebo groups at this time.

Fahy, et al. (1993) suggest that reduction of bulimic symptomatology by dexfenfluramine may have been submerged in the therapeutic effects of the cognitive-behavioural therapy. They postulate that because of the heterogeneity of bulimics as a group, some may respond to brief educational interventions, some intensive psychotherapy, and non-responders to psychological intervention may respond to medication. However, their most conservative interpretation of their results is that the drug dexfenfluramine is not effective in treating primary bulimic symptomatology, nor mood-dependent improvement in abnormal eating behaviours.

Fahy et al. (1993) compare the low drop-out rate (9%) in this study to others that include psychotherapy and contrast it to the 40% drop-out rate experienced in the Russell et al. (1988) study they describe as a study of dexfenfluramine or placebo alone. However, the methods section of the 1988 study informs the reader that the patients were given "dietary advice and supportive psychotherapy over the course of 1 h interviews. This treatment was supportive, educative, and contained elements of cognitive therapy although falling short of the intensive form of this treatment recommended by Fairburn". The psychotherapy provided in the 1993 study is described as "cognitive-behavioural psychotherapy which was an abbreviation of the method developed by Fairburn and

colleagues". More detail is given on the educational and behavioural interventions in this methods section than in the 1988 article. Perhaps this reflects an increase in magnitude of psychotherapy, however since details of the two procedures cannot be compared and no time allotment in the more recent study is stated, one can only assume that this is the reason these authors have chosen to discount or ignore the therapeutic intervention in the earlier study.

Evidence that history of dieting may promote serotonin dysregulation

Since it is not possible to study bulimic patients before onset of the disorder it is difficult to determine whether neurochemical abnormalities existed prior to bulimic behaviour or are a result of the behaviour. However, numerous studies have shown that reduced calorie intake causes multiple neuroendocrine changes (see Fichter, 1992 for a review; Goodwin, Fairburn, & Cowen, 1987) and it is possible that these changes contribute to the onset of eating disorders in vulnerable individuals.

Anderson, Parry-Billings, Newsholme, Fairburn & Cowen (1990) subjected nine women and six men to calorie restricted diets for 3 weeks. Subjects were of average weight at the commencement of the study. Neuroendocrine testing was carried out before and at the end of the third week of dieting. Dieting decreased plasma total tryptophan levels after an overnight fast for both sexes and

significantly more for women. There was a significant tryptophan/branch chain amino acid ratio decline, however, this decrease did not reach significance for the groups separately. Prior to dieting tryptophan infusion resulted in a large increase in plasma total tryptophan for both sexes. After dieting this increase was smaller in women whereas it was unchanged in men. Prolactin response to tryptophan infusion was significantly enhanced in women after dieting. No change in response was found in men. These authors conclude that dieting alters brain serotonin function in women in response to decreased availability of plasma tryptophan.

Rationale and Hypotheses

Research suggests that there is a biological component to bulimia nervosa. Many bulimic patients suffer from depression, disinhibition, and carbohydrate cravings and report reduced feelings of satiety after a meal. Each of these symptoms have been connected to dysregulation of serotonin function and it has been suggested that abnormal serotonin function plays a role in the onset and/or maintenance of bulimia nervosa. Research indicates that bulimics show altered serotonergic metabolism and response.

Pharmacologic treatments particularly antidepressant medication, have been effective in reducing bulimic symptomatology. It has not been determined whether symptoms are alleviated via direct impact of these drugs on the food

intake mechanisms or via their antidepressant properties. Some of these agents enhance serotonergic transmission, one neurochemical known to be involved in the control of food intake. Dexfenfluramine is specific to the serotonergic system and unlike antidepressants both inhibits uptake and enhances release of the neurotransmitter. Research has shown that this drug reduces food intake and there is some evidence that dexfenfluramine is effective in reducing bulimic symptomatology. Dexfenfluramine is expected to reduce bulimic symptomatology through enhanced feelings of satiety that reduce binge frequency and/or binge size. A reduction in purging frequency would be expected to follow binge effects.

The most frequent antecedent to bulimia nervosa is food restriction. Reduced calorie intake causes multiple neuroendocrine changes and has been found to alter serotonin function in women. Certain dieting behaviours such as fasting and carbohydrate restriction combined with measures of severity and duration may predict level of response to dexfenfluramine.

Hypothesis:

1. Dexfenfluramine will reduce binge size as a result of increased feelings of satiety.
2. Binge and purge frequency will be reduced.
3. Reduction of bulimic symptomatology will not be related to alleviation of depression.

4. Diet history will predict response to dexfenfluramine.

Method

Procedure

The data employed in this study were collected at the Eating Disorders Clinic at the Ottawa Civic Hospital as part of a study on the effect of carbohydrate binging and stress on dexfenfluramine response in bulimia nervosa. Eighty-five normal weight female volunteers who met DSM-III-R criteria for bulimia nervosa, confirmed by clinical assessment and interview, were included in the trial. No subjects were pregnant or lactating, suicidal, suffering from physical illness, nor dependent on alcohol or other drugs. All were free of prescribed psychotropic medication for 7 days prior to and during the study. Subjects did not receive psychotherapeutic counselling during the course of the study.

Subjects completed the Diagnostic Schedule of Eating Disorders (DSED, Johnson, 1985), the Diagnostic Interview Schedule (DIS, Robins, Helzer, Ratcliffe et al., 1981), the Eating Disorders Inventory (EDI, Garner, Olmsted & Polivy, 1983), the Hopkins 90-item Symptom Checklist Revised (SCL-90-R, Derogatis, 1977; the Beck Depression Inventory (BDI, Beck, Ward & Mendelson, 1961), the Daily Hassles Scale (DHS) and Daily Uplift Scale (DUS) (Kanner, Coyne, Schaefer & Lazarus, 1981), the Social Readjustment Rating Scale, (SRRS,

Holmes and Rahe, 1967), and the State Trait Anxiety Inventory (STAI, Spielberger, 1983) as part of a preliminary assessment. (See Appendix I for a description of these measures). Subjects also completed a modification of the DSED section addressing composition of binge food, Binge Food Record (BFR) (Appendix II), to measure frequency of bingeing on foods of differing macronutrient composition.

Eighty-five subjects were randomly allocated to receive orally either dexfenfluramine (30 mg/day, Servier) or equivalent placebo in a double blind fashion for a 2-week period. Subjects were instructed to take the tablets at bedtime and in the morning when bingeing and vomiting is less frequent. Unused pills were returned in their containers at the end of the 2-week period and blood levels of dexfenfluramine were measured at the end of Week 1 in order to measure compliance.

Bulimic symptoms, psychological status, and binge macronutrient content were monitored for 7 days pre-drug administration as a baseline, during the 14 days drug administration, and for 7 days following the drug trial to assess rebound effects and possible withdrawal depression. Subjects completed the Daily Binge Record (Appendix III) (Blouin et al., 1988). The caloric and macronutrient content of binges recorded in the Daily Binge Record were calculated using a computerized nutritional analysis program. The EDI, the BDI and the SCL-90-R were

administered on days 0, 7, 14, 21 and 28. Subjects also completed the Bulimic Symptom Checklist (BSC) at days 0, 7, 14, and 28 in order to monitor binge and purge frequency over each 7-day period. Subjects were weighed and monitored for adverse reaction to the medication and menstruation was also monitored.

Data Analysis

Prior to analysis variables were examined through various SPSS programs for missing values, normalcy, linearity, and the presence of outliers. The variables were examined separately for the dexfenfluramine group and the placebo group. Skewness and kurtosis were evaluated using a criterion of z score 3.67 above or below zero ($p=.001$). Cases with standardized scores in excess of plus or minus 3.67 were considered to be univariate outliers. Multivariate outliers were identified according to Mahalanobis distance criterion of $p<.001$.

The Bulimic Symptom Checklist provides measures of binge, vomit and laxative use frequency over a one week period. Difference from baseline variables were created for binge frequency. These variables were calculated by subtracting baseline measures from Week 1, Week 2 and Post-treatment measures. Since 20% of both groups did not engage in vomiting and less than 20% reported using laxatives, vomit and laxative frequency differences were not included as separate variables. A new variable was created by

combining binge frequency and vomit frequency into a total symptoms score and then difference from baseline variables were created by subtracting baseline measures from Week 1, Week 2 and Post-treatment measures.

The dexfenfluramine group and the placebo group were compared on binge differences and total symptom differences using repeated measures analysis of variance with the within-subjects effect of week (baseline to Week 1 and baseline to Week 2). Significant results were followed by t-tests. Post-treatment measures address the issue of rebound rather than treatment effect and therefore were analyzed separately using univariate t-tests.

The Daily Binge Record provides daily frequencies of binge, vomit, laxative use, and the caloric content of binges. Daily binges were summed over three one week periods - baseline to Week 1, Week 1, and Week 2 - providing three repeated binge frequency measurements. Similar variables were created for vomit and laxative counts. Calorie counts for each day were divided by binge frequency for that day, and averaged across each 7-day period producing three repeated calories/binge variables. Vomit and laxative frequency variables were not included in further analysis because of large percentages of missing values or zero values. Multivariate analyses of variance was conducted examining the between group effect and the within-subjects effect of week on binge frequency and

calories/binge.

A binge difference variable was created by subtracting baseline measures of binging from Week 1, Week 2 and Post-treatment measures. Change in binge frequency was examined using repeated measures analysis of variance and significant results were followed by t-tests.

Multivariate repeated measures analysis was conducted on Beck Depression Inventory scores to examine the between group effect and the within-subjects effect of week on depression. BDI scores at the end of Week 1, Week 2 and Post-treatment were regressed on binge difference scores from the Bulimic Symptom Checklist to explore the relationship between binge change and depression.

In order to test the hypothesis that diet history would predict response to dexfenfluramine treatment measures of duration and severity of dieting were taken from the DSED. Duration of dieting practices, was represented by a variable calculated by subtracting the age of first diet from the current age. Severity of dieting was represented by answers to the DSED question concerning preferred method of dieting. Each method was rated on a 9-point scale from 1=most preferred to 9=least preferred. Choices were: skip meals; completely fast; restrict carbohydrates; restrict sweets; restrict fats.

Three variables were created by subtracting current weight from the highest weight, current weight from the

lowest weight and highest weight from lowest weight to represent weight fluctuation history, an outcome of dieting practices.

Standard multiple linear regressions were performed between binge difference (Daily Binge Record and Bulimic Symptom Checklist) as the dependent variables and number of years dieting, preferred methods of dieting, and difference from highest to current weight.

Exploratory analysis of the effect of dexfenfluramine on the cognitive aspects of bulimia were performed using measures from the EDI. Scores on measures of drive for thinness, bulimia (urge to binge and purge), body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, and maturity fears taken at baseline, one and two weeks post treatment were analyzed separately with repeated measures multivariate analysis. Psychiatric measures of somatization, obsessive-compulsive tendencies, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, psychoticism, loss of appetite, overeating and guilt from the SCL-90-R were also examined for response to drug administration.

Results

Group characteristics

One subject assigned to the dexfenfluramine group and four subjects assigned to the placebo group dropped out of the study for personal reasons leaving 80 of the 85 subjects initially recruited. Characteristics of the dexfenfluramine and placebo groups appear in Table 1. Despite double blind random assignment of subjects to groups the dexfenfluramine and placebo groups differed significantly in symptom severity. The active drug group reported significantly higher frequencies of bingeing ($\bar{X}=7.29$) than the placebo group ($\bar{X}=5.15$), $t(79)=2.28$, $p<.026$, at Baseline. No other significant differences between the dexfenfluramine and placebo groups were observed prior to treatment.

Weekly Bulimic Symptom Checklist

The Bulimic Symptom Checklist Record provides frequencies of binge, vomit, and laxative use in one week. Frequency counts revealed that only eight subjects in the active drug group, and five subjects in the control group reported using laxatives as a method of purging. This measure was not included in further analysis. No measures exceeded skewness or kurtosis criterion, however visual inspection of the distributions revealed that the vomit measure departed from normality because of the frequency of

Table 1

Characteristics of Dexfenfluramine and Placebo Groups

	D-FF (n=41)		Placebo (n=39)	
	Mean	SD	Mean	SD
Current age	24.2	5.48	25.1	5.27
Age of first diet	13.8	2.90	14.6	3.39
Current weight (kg)	68.1	21.33	69.1	14.18
Highest weight (kg)	72.8	24.24	69.4	13.13
Height (cm)	158.6	26.49	158.8	26.10
Binge episodes/week	7.3	5.18	5.2	3.02
Vomit episodes/week	6.3	6.44	4.3	4.47
BDI	15.9	8.67	16.5	9.58

zero values. Eight subjects (20%) in each group reported zero vomiting episodes at all four measurement times. For this reason, binge count was considered to be a more informative measure. Group means on bulimic symptoms from the Bulimic Symptom Checklist are presented in Table 2.

Group means replaced missing values for 10.4% of binge and vomit frequency. Baseline data were missing for three subjects and these cases were not included in the analysis. No univariate outliers were found on the baseline Binge/Vomit measures. One value in the dexfenfluramine group exceeded criterion in the Week 2 binge measure, but since the outlier could have been considered part of the treatment effect, the case was not deleted. Similar results were found in screening the vomit scores, with one value on the Week 1 measure and one on the Week 2 measure exceeding criterion. Both cases were in the dexfenfluramine group.

A 2 x 2 mixed design analysis of variance was performed on binge differences. Results indicate a significant drug effect (dexfenfluramine versus placebo), $F=8.09$, $df=1,75$, $p<.006$, and no Group by Week interaction (see Figure 1). The active drug group reported significantly greater reductions in bingeing after one week of dexfenfluramine administration ($\bar{X}=-3.04$) than the control group ($\bar{X}=-.14$), $t(75)=-3.08$, $p<.003$. Binge reduction at the end of two weeks for the active drug group ($\bar{X}=-2.3$) was not significantly different from the placebo group's reduction

Table 2

Group Means on Bulimic Symptoms (Weekly Bulimic Symptom Checklist)

Group	Week		
	Pre	Week 1	Week 2
Binge Frequency			
D-FF	7.29	4.44	5.18
Placebo	5.15	4.82	4.03
Vomit Frequency			
D-FF	6.29	4.11	4.35
Placebo	4.31	4.05	3.57
Binge Difference			
D-FF		-3.04	-2.30
Placebo		-0.14	-0.81
Total Symptom Difference			
D-FF		-4.41	-4.51
Placebo		-0.30	-1.46

Figure 1. Change in binge frequency from Baseline to Week 1 and Week 2 on dexfenfluramine and placebo from the Weekly Bulimic Symptom Checklist. Error bars represent standard errors of the mean.

$(\bar{X}=-.81)$, $t(75)=-1.85$, $p<.069$.

One outlier on the total symptom change variable was deleted from the dexfenfluramine group. The results of total symptom change from pre-treatment to Week 1 and to Week 2 are summarized in Figure 2. A 2 X 2 analysis of variance of total symptom differences revealed a significant group effect, $F=6.02$, $df=1,74$, $p<.017$. There was no Group X Week interaction. Subjects receiving dexfenfluramine reported significantly greater symptom reduction after one week drug administration ($\bar{X}=-4.41$), ($t(74)=-2.75$, $p<.007$) than subjects receiving placebo ($\bar{X}=-.30$). Total symptom reduction for the active drug group ($\bar{X}=-4.51$) approached significance ($\bar{X}=-1.46$) when compared to the placebo group at the end of Week 2, $t(74)=-1.92$, $p<.059$.

Post-Treatment Analysis

Pairwise t-tests revealed that binge differences were not significantly different for Post-treatment and Week 1 treatment measurements, $t(76)=.15$, $p<.884$. A between groups t-test of Post-treatment measurement indicated that the groups did not differ at this time, $t(75)=-.93$, $p<.355$. Subjects receiving dexfenfluramine continued to report binge reduction ($\bar{X}=-2.14$) as did subjects receiving placebo ($\bar{X}=-1.28$). Results of binge differences from baseline to Week 1, Week 2 and Post-treatment are summarized in Figure 3.

Similar results were found for the total symptom difference, $t(75)=.46$, $p<.65$. The dexfenfluramine group

Figure 2. Change in total symptoms, consisting of binge and vomit frequencies, from Baseline to Week 1 and Week 2 on dexfenfluramine and placebo from the Weekly Bulimic Symptom Checklist. Error bars represent standard errors of the mean.

Figure 3. Change in binge frequency from Baseline to Weeks 1 and Week 2 on dexfenfluramine and placebo, and one week post treatment from the Weekly Bulimic Symptom Checklist. Error bars represent standard errors of the mean.

continued to report reductions in total symptomatology from Pre-treatment assessment ($X=-3.36$) as did the placebo group ($X=-2.17$) $t(74)=.70$, $p<.488$. (See Figure 4).

Daily Binge Record

The one missing value in each group on binge frequency was replaced by the group mean. No cases were univariate outliers and distribution of this variable did not depart significantly from normality, and no transformation was required. Vomit frequency was deleted since 28 subjects (35%) reported zero vomits at baseline and 41 values (17%) were missing over the three measures. Similar to the Bulimic Symptom Checklist, it was found that only four subjects in the active drug group, and five subjects in the control group reported using laxatives as a method of purging. This measure was not included in further analysis.

Subjects who did not report bingeing were assigned a zero value in the corresponding calorie/binge variable. Group means were substituted for one missing Week 2 value in each group. No cases were univariate outliers. One case in the placebo group was missing all calorie/binge values and this case was deleted leaving 41 cases in the dextrofenfluramine group and 39 cases in the placebo group. Group means on bulimic symptoms from the Daily Binge Record are presented in Table 3. Distributions of the calorie/binge variable departed significantly from

Figure 4. Change in total symptoms, consisting of binge and vomit frequencies, from Baseline to Week 1 and Week 2 on dexfenfluramine and placebo, and one week post treatment from the Weekly Bulimic Symptom Checklist. Error bars represent standard errors of the mean.

Table 3

Group Means on Bulimic Symptoms (Daily Binge Record)

Group	Week		
	Pre	Week 1	Week 2
Binge Frequency			
D-FF	5.39	6.05	5.90
Placebo	5.03	3.95	3.55
Calories/Binge			
D-FF	1165.20	1310.24	1229.18
Placebo	1098.63	1044.60	1135.18
Binge Difference			
D-FF		.66	.51
Placebo		-1.08	-1.47

normality, $z > 3.67$, $p < .001$, and square root transformation was applied.

No multivariate outliers were identified. Multivariate analysis of binge frequency and calories/binge revealed that the DVs were not significantly affected by group membership or Week, $F=0.88$, $df=2,76$, $p < .418$), nor by their interaction $F=2.26$, $df=4,74$, $p < .071$, (See Figures 5 and 6).

Repeated measures analysis of variance of binge change revealed a significant group effect, $F=6.05$, $df=1.78$, $p < .016$). The placebo group reported reductions ($\bar{X}=-1.08$) in binge frequency while the dexfenfluramine group reported an increase ($\bar{X}=.66$), $t(78)=2.53$, $p < .014$, after one week of treatment, and again after two weeks ($\bar{X}=-1.47$) vs. ($\bar{X}=.51$), $t(78)=1.99$, $p < .05$, (See Figure 7).

Summary of Primary Bulimic Behaviour Results

Weekly reports of bulimic behaviour demonstrated that dexfenfluramine was more effective than placebo in reducing bulimic symptomatology one week after first administration. This trend continued, although the placebo group also reported reductions in symptomatology by the end of the second week. Binge and purge frequency continued to be reduced post-treatment for both groups.

The daily recordings of foods consumed during each binge did not reflect the same effect. According to this measure, subjects receiving active drug increased bingeing activity, while the placebo group improved. The average

Figure 5. Binge frequency at Baseline, and Weeks 1 and 2 of the treatment phase from the Daily Binge Record. Error bars represent standard errors of the mean.

Figure 6. Mean calories per binge at Baseline, Weeks 1 and 2 of the treatment phase from the Daily Binge Record. Error bars represent standard errors of the mean.

Figure 7. Change in binge frequency from Baseline, to Week 1 and Week 2 on dexfenfluramine and placebo from the Daily Binge Record. Error bars represent standard errors of the mean.

number of calories consumed during a binge was not affected.

Beck Depression Inventory

No significant group effect nor interaction was found in 2 x 3 repeated measures analysis of variance of scores on the BDI. The within subjects variable Week was significant, $F=76$, $df=2$, $p<.001$. Baseline ($\bar{X}=16.05$) measures were different from those at Week 1 ($\bar{X}=13.46$), $t(81)=3.30$, $p<.001$, Week 2 ($\bar{X}=13.23$), $t(79)=3.67$, $p<.000$. Depression ratings for both groups declined significantly from baseline throughout the treatment phase (See Figure 8). While the dexfenfluramine group tended to rebound after discontinuation of drug therapy, the active drug group's mean BDI ($\bar{X}=14.66$) was not significantly different from the placebo group's mean BDI ($\bar{X}=11.22$) $t(75)=1.71$, $p<.092$. The dexfenfluramine treated group BDI scores at the end of one week of drug administration were not significantly correlated with binge difference scores for the dexfenfluramine group $r=.30$, $F=3.774$, $df=1,37$, $p<.600$, nor for the placebo group $r=.17$, $F=1.04$, $df=1,35$, $p<.314$. Depression scores after the second week of drug therapy were significantly correlated with binge difference scores for the dexfenfluramine group $r=.52$, $F=14.058$, $p<.006$ but not for the placebo group $r=.02$, $F=.012$, $df=1,35$, $p<.913$. At the post-treatment measure, BDI scores were again significantly correlated with binge change scores for the dexfenfluramine group $r=.36$, $F=5.769$, $p<.021$ but not for the

Figure 8. Beck Depression Inventory scores at Baseline, Weeks 1 and 2 on dexfenfluramine and placebo, and one week post treatment. Error bars represent standard errors of the mean.

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placebo group $\bar{r}=.05$, $F=.074$, $df=1,32$, $p<.788$.

Summary of Beck Depression Inventory Results

According to scores on the Beck Depression Inventory, both groups were moderately depressed at commencement of the study, and showed substantial improvement in mood by the end of the first week. The placebo group continued to report diminishing depressive symptomatology through to post-treatment, while the dexfenfluramine group tended to become more depressed. Depressive symptomatology was not significantly correlated with changes in binge frequency measured by the Bulimic Symptom Checklist for either group after one week of drug administration. At the end of the second week, however, level of depression was significantly correlated with reduction in binge frequency in the dexfenfluramine group. Change in binge frequency from Baseline to Post-treatment was also correlated with depressive symptomatology for this group.

Prediction of Response

Group means were substituted for missing number of years dieting values for three cases in the dexfenfluramine group and two cases in the placebo group. Missing values for six cases in the placebo group on the difference from highest weight variable were substituted by group means. Sixteen values (20%) on the difference from current to lowest weight and highest to lowest weight variables were missing because subjects did not provide an answer to the

lowest weight question. Weight differences from lowest weight were not included in regression analysis. Two cases were dropped from analysis, one because of missing values, and one due to meeting Mahalanobis distance outlier criterion. Group means on predictor variables are presented in Table 4.

A standard multiple regression was performed between the Weekly Symptom Checklist binge difference variable as the dependent variable and number of years dieting, difference from highest to current weight, and preferred methods of dieting as the independent variables. Diet history did not predict binge reduction $R=.44568$, $F=.921$, $df=7,26$, $p<.507$. Similar results were found when total symptom differences was the dependent variable $R=.44754$, $F=.930$, $df=7,26$, $p<.500$.

A standard multiple regression was performed between the Daily Binge Record binge difference variable as the dependent variable and number of years dieting, difference from highest to current weight, and preferred methods of dieting as the independent variables. Diet history did not predict the change in binge behaviour $R=.37953$, $F=.64907$, $df=7,27$, $p<.712$.

None of these predictors were significantly correlated with the DVs (See Tables 5 and 6).

Summary of Prediction of Response Results

Diet history did not predict bulimic symptomatology

Table 4

Group Means on Predictor Variables

	D-FF		Placebo	
	Mean	SD	Mean	SD
Years Dieting	10.4	6.31	10.4	5.38
Weight Change (kg)	- 4.9	18.72	- 0.7	13.55
Skip Meals	4.6	3.23	4.3	3.10
Completely Fast	6.6	3.05	6.0	2.87
Restrict Carbohydrates	5.4	2.67	5.9	2.29
Restrict Sweets	3.5	2.75	4.6	3.04
Restrict Fats	3.8	2.71	4.6	2.70

Table 5

**Correlation of Individual Predictors on Weekly Bulimic
Symptom Checklist Dependent Variables**

Predictor	Dependent Variables					
	Binge Dif.			Total Symptoms		
	R	² R	p<	R	² R	p<
Years Dieting	.181	.033	.27	.179	.032	.28
Weight Change	.148.	.022	.37	.155	.024	.35
Skip Meals	.294	.087	.08	.233	.054	.17
Completely Fast	.091	.009	.59	.133	.018	.44
Restrict Carb.	.008	.000	.97	.001	.000	.99
Restrict Sweets	.075	.006	.67	.049	.002	.78
Restrict Fats	.080	.006	.65	.021	.001	.90

Table 6

Correlation of Individual Predictors on Daily Binge Record
Dependent Variables

Predictor	Dependent Variable		
	Binge Dif.		
	R	²	p<
		R	
Years Dieting	.14227	.02024	.38
Weight Change	.16186	.02620	.28
Skip Meals	.02530	.00064	.88
Completely Fast	.02747	.00075	.87
Restrict Carb.	.14650	.02146	.49
Restrict Sweets	.16141	.02605	.35
Restrict Fats	.31933	.10197	.06

changes as measured by the Weekly Symptom Checklist or the Daily Binge Record. Number of years dieting, difference from highest to current weight and preferred methods of dieting were unrelated to changes in bulimic behaviour during the study.

Exploratory Analyses

Cognitive Effects. Separate 2 X 3 repeated measures multivariate analysis of variance were performed for each EDI subscale for the treatment phase of the study. Post-treatment measure were analyzed using univariate t-tests.

On the bulimia scale there was no significant difference between groups but the within subjects effect of Week was significant $F=3.50$, $df=2,67$, $p<.036$. Subjects in both groups experienced a reduction in the urge to binge from Baseline ($\bar{X}=9.732$) to the end of Week 1 ($\bar{X}=8.690$) $t(70)=2.66$, $p<.010$. At the end of the second week of drug administration, the mean urge to binge ($\bar{X}=13.338$) was significantly higher $t(73)=-5.43$, $p<.000$ than at baseline and at the end of Week 1 $t(70)=-6.53$, $p<.000$. The interaction between Group and Week was not significant $F=.33$, $df=2,67$, $p<.719$ indicating a similar pattern in the urge to binge for placebo and active drug groups. Groups did not differ at Post-treatment measurement.

The effect of week was also significant for the ineffectiveness subscale during drug treatment $F=3.18$, $df=2,67$ $p<.048$. Feelings of ineffectiveness significantly

decreased ($X=8.16$ to $X=7.24$) $t(70)=2.56$, $p<.013$ during the first week of drug administration. Mean ratings of ineffectiveness at the end of Week 2 ($X=7.03$) were also significantly lower than baseline ratings $t(73)=2.13$, $p<.037$. Once again the Group X Week interaction was non-significant $F=.877$, $df=2,67$, $p<.42$. There was no difference between groups at Post-treatment measure.

Although both groups tended to improve scores on the interoceptive awareness subscale for the sample as a whole were not significantly different across the treatment phase of the study $F=2.723$, $df=2,67$, $p<.073$, nor did the groups differ $F=.04$, $df=1,68$, $p<.840$. While the placebo group continued to improve during the post-treatment week ($X=5.73$) and the dexfenfluramine group reported enhanced interoceptive awareness ($X=7.23$), the difference between groups was not significant $t(71)=1.06$, $p<.291$.

There were no significant Group or Week effects, or Group X Week interactions for measures of drive for thinness, body dissatisfaction, perfectionism, interpersonal distrust, or maturity fears.

Psychiatric Effects. Separate 2 X 3 multivariate repeated measures analyses of variance were performed for SCL-90-R measures for the treatment portion of the study. Post-treatment measures were analyzed using univariate t-tests.

Analysis of the somatization subscale revealed

significant Group $F=7.76$, $df=1,75$, $p<.007$ and Week $F=6.37$, $df=2,74$, $p<.003$ effects but no Group X Week interaction for the treatment period. The placebo group's scores were significantly lower than the dexfenfluramine group's scores at baseline ($\bar{X}=.472$ vs $\bar{X}=.681$) $t(82)=2.21$, $p<.030$, after week 1 ($\bar{X}=.424$ vs $\bar{X}=.694$) $t(78)$, $p<.011$, after week 2 ($\bar{X}=.328$ vs $\bar{X}=.611$) $t(78)$, $p<.002$. Both groups somatization symptoms were reduced from Baseline ($\bar{X}=.593$) to Week 2 ($\bar{X}=.472$) $t(78)=2.85$, $p<.006$. Symptoms were also evaluated as significantly less severe at Week 2 than at Week 1 ($\bar{X}=.565$) $t(77)=3.22$, $p<.002$. The placebo group's Post-treatment scores ($\bar{X}=.338$) were significantly lower than the active drug group's scores ($\bar{X}=.653$) $t(75)=3.36$, $p<.001$.

Obsessive compulsive tendencies declined for the sample as a whole, resulting in a significant Week effect $F=7.827$, $df=2,74$, $p<.001$ for the treatment weeks. The drop in scores on the obsessive compulsive subscale from Baseline ($\bar{X}=.891$) to the end of the second week of drug treatment ($\bar{X}=.656$) was significant $t(78)=3.38$, $p<.001$. Measurement at the end of week 2 was also significantly lower than at the end of the first week ($\bar{X}=.786$) $t(77)=2.68$, $p<.009$. Neither the Group effect nor the Group X Week interaction were significant. Groups were not significantly different at the Post-treatment measure.

There was also a significant Week effect for the interpersonal sensitivity subscale $F=3.544$, $df=2,74$, $p>.034$

for the treatment portion of the study. Interpersonal sensitivity scores fell significantly from baseline ($\bar{X}=1.270$) to Week 1 ($\bar{X}=2.230$) $t(78)=2.03$, $p<.046$. Scores at Week 2 ($\bar{X}=1.058$) were also significantly lower than at baseline $t(78)=2.84$, $p<.006$. Group scores were not significantly different during the treatment phase, or post treatment, and there was no Group X Week interaction.

Scores on the depression subscale were significantly different across the treatment phase of the study $F=6.45$, $df=2,74$, $p<.003$. Depressive symptoms for at Baseline 1 ($\bar{X}=1.196$) were significantly decreased by Week 1 ($\bar{X}=1.030$) for both groups. Depression scores at the end of Week 2 ($\bar{X}=.946$) were also significantly lower than baseline scores $t(78)=3.66$, $p<.000$. However, the dexfenfluramine group was significantly more depressed ($\bar{X}=1.266$) than the placebo group ($\bar{X}=.903$) $t(75)=2.07$, $p<.039$ one week after pharmacotherapy was discontinued.

Subjects' feeling of hostility changed significantly over the treatment period $F=4.101$, $df=2,74$, $p<.020$. Both groups rated themselves as less hostile at Week 1 ($\bar{X}=.569$) than at Baseline ($\bar{X}=.734$) $t(78)=2.93$, $p<.004$ and although mean ratings at the end of week 2 ($\bar{X}=.601$) were slightly higher than after the first week, they were still significantly lower than at Baseline $t(78)=2.03$, $p<.046$. There were no significant Group or Group X Week effects, and the groups were not significantly different post treatment.

There was a significant Group X Week interaction $F=4.049$, $df=2,74$, $p<.021$ for the psychoticism subscale. The dexfenfluramine group's scores declined significantly from Baseline ($\bar{X}=.50$) to Week 1 ($\bar{X}=.38$) $t(38)=2.16$, $p<.037$ but then tended to increase. The placebo group's feelings of alienation declined significantly from Baseline ($\bar{X}=.69$) to Week 3 ($\bar{X}=.30$) $t(37)=2.18$, $p<.036$. Scores at Week 3 were also significantly lower than at Week 2 ($\bar{X}=.43$) $t(38)=2.90$, $p<.006$. After discontinuation of drug therapy the placebo group felt significantly less alienated ($\bar{X}=.263$) than the dexfenfluramine group ($\bar{X}=.549$) $t(75)=2.77$, $p<.005$.

Analysis of ratings of loss of appetite during the study revealed significant Group $F=5.51$, $df=1,75$, $p<.022$ and Week $F=4.785$, $df=2,74$, $p<.011$ effects but no Group X Week interaction. Both groups reported more loss of appetite at Week 1 ($\bar{X}=.747$) than at Baseline ($\bar{X}=.430$) $t(78)=-3.08$, $p<.003$. Loss of appetite scores were significantly lower at Week 2 ($\bar{X}=.46$) $t(77)=2.63$, $p<.010$. The dexfenfluramine group reported significantly greater loss of appetite at Week 2 ($\bar{X}=.781$) than the placebo group ($\bar{X}=.180$) $t(78)=3.47$, $p<.001$. Between group differences were not significant at Post-treatment measurement.

There was a significant Week effect for the Overeating subscale $F=13.325$, $df=2,74$, $p<.000$. All subjects rated their overeating lower after one week of the study ($\bar{X}=2.152$) $t(78)=4.11$, $p<.000$, and after the second week of the study

($\bar{X}=2.06$) $t(78)=4.95$, $p<.000$ than at Baseline ($\bar{X}=2.772$).

There was no significant Group effect nor a Group X Week interaction. Groups were not different post treatment.

There were no significant Group or Week effects on the measure of guilt, nor was there an interaction for the treatment phase. After the drug phase the placebo group experienced a drop in guilt feelings and their scores at this time ($\bar{X}=1.286$) were significantly lower than at baseline ($\bar{X}=1.800$) $t(34)=2.28$, $p<.029$. Although the placebo group tended to experience decreased feelings of guilt post treatment ($\bar{X}=1.36$) while the active group felt more guilt ($\bar{X}=2.83$) than during the treatment phase, the between group difference was not significant $t(70)=1.61$, $p<.113$.

There were no significant Group, Week, or Group X Week interactions for the anxiety, or phobic anxiety subscales.

Summary of Cognitive and Psychiatric Results

No effect of dexfenfluramine on the cognitive urge to engage in bulimic behaviour was evident. The desire to binge followed the same pattern for both groups. After an initial reduction, the urge to binge increased to a level that was stronger than baseline measurement, and then dropped to the original degree. As might be expected, feelings of ineffectiveness decreased as binge frequency diminished. Interoceptive awareness improved for both groups during the drug phase, but the dexfenfluramine group experienced a rebound of difficulties following drug

discontinuation.

The active drug group was significantly more concerned with bodily functions than the placebo group from the beginning to the end of the study, but both groups experienced improvement in somatization over the treatment phase. Obsessive compulsive tendencies were also reduced in both the dexfenfluramine group and the placebo group. Subjects suffered progressively less interpersonal sensitivity throughout the study. Depressive symptoms measured by the SCL-90-R mirrored the BDI results. Subjects also felt less hostile and alienated as the study progressed however, the dexfenfluramine group experienced a return of feelings of depression and alienation by the Post-treatment assessment.

Subjects taking dexfenfluramine experienced a greater loss of appetite than those taking placebo and this effect did not continue post treatment. Both groups reported progressively less overeating. Feelings of guilt for both groups followed the same trajectory as the urge to binge during the drug phase. An initial reduction was followed by increased levels at Week 2. However the dexfenfluramine group experienced a rebound post treatment while the placebo group's guilt was reduced.

Discussion

This study found that dexfenfluramine reduced binge behaviour in a bulimic sample. This finding is consistent with the interpretation that enhancing serotonin activity is effective in reducing binge behaviour in a bulimic sample. This is in keeping with the finding that modifying serotonin function by administering fenfluramine influences binge eating behaviour among bulimic subjects in a laboratory setting (Robinson et al., 1985). In the present study, the decreased binging over a two-week period during dexfenfluramine treatment is compatible with the reduced binge size and frequency that was reported by Robinson et al. (1985) following acute administration of fenfluramine to bulimic subjects. The observed decreases in total symptomatology, binging and purging one week after administration are consistent with the results of Blouin et al. (1988) and Russell et al. (1988). Robinson et al. (1985) and Blouin et al. (1988) suggested that fenfluramine exerts its antibulimic effects activating central serotonin activity thereby inducing satiety. It has also been proposed that bulimia may be associated with reduced serotonergic mechanisms which results in diminished satiety, and the promotion of binge eating. This interpretation is in keeping with previous research indicating that bulimic patients show altered serotonin metabolism and response to test meals and serotonin agonists (Brewerton et al., 1990;

Goldbloom et al., 1990; see Jimerson et al., 1990 for a review; Kaye et al., 1984) and that bulimic patients report difficulty knowing when they are full (Halmi, 1988).

The pattern of eating in bulimia nervosa also suggests that an aberration in the perception in satiety may be present. Bulimic patients do not report a normal decline in hunger and an increase in satiety during or following a meal. They often consume more as they eat rather than less (see Halmi, 1990 for a review). Robinson et al. (1985) found that bulimics report greater hunger following food ingestion than do controls. Blouin et al. (1993) found that bulimic patients, following IV administration of glucose reported an enhanced urge to binge eat and negative mood state, whereas controls did not. Measures of and tryptophan/LNAA did not differ between bulimia patients and controls in this latter study so it is unlikely that peripheral alteration of tryptophan/LNAA is directly associated with the increased urge to binge. Blouin et al. (1993) also found that blood glucose levels were slightly lower in bulimics than controls, although not significantly lower at peak glucose levels, and bulimics failed to experience the normal drop in blood glucagon that is expected following elevation of blood glucose. Considering that blood glucose and insulin levels of bulimics were very close to those of controls, it appears that bulimic patients experienced abnormal psychological responses to their

changes in system blood glucose. Blouin et al. (1993) concluded that bulimics have an abnormal central response to glucose challenge other than peripheral responses, and they hypothesized that this involved central serotonin. Since serotonin activity has been linked to both food-intake regulation and mood, its involvement would be consistent with the interpretation of abnormal psychological response to peripheral glucose elevation.

Previous research indicates that bulimic patients report greater seasonal variation in weight gain and eating than do normal controls (Blouin et al., 1992). Seasonal variation has been found in hypothalamic serotonin levels (Carlsson, Svennerholm, & Winblad, 1980). The low levels of serotonin during the winter months, and high levels in the spring and fall coincide with reported increases and decreases in binge eating in bulimia nervosa patients. Blouin et al. (1992) suggest that the seasonal effects in bulimia nervosa are mediated through seasonal variations in central serotonergic mechanisms and that this effect may be associated with the serotonergic regulation of food intake mechanisms.

Dexfenfluramine is a pure serotonin agonist devoid of dopaminergic or sympathomimetic activity. Dexfenfluramine has a long history of reducing food intake in animals and humans. Animal studies reveal that reduction in the amount of food consumed is achieved by reducing meal size and

eating rate, while the frequency of eating is unaltered. Human studies confirm these findings. Administration of dexfenfluramine produced a satiating effect, reducing the motivation to eat and meal size (see McTavish & Heel, 1992, for a review).

The response to dexfenfluramine is similar to the effect of injecting serotonin directly into the paraventricular nucleus of the hypothalamus. After injection, food intake is reduced primarily through a decrease in meal size and duration. Neither the latency to meal onset nor the frequency of meals is altered. The lack of effect on initiation of eating suggests that dexfenfluramine affects eating by termination of feeding though the induction of satiety, rather than by reducing the initiation of feeding through suppression of hunger (Leibowitz, Weiss, & Shor-Posner, 1987).

It has been theorized that the mechanism of action of dexfenfluramine is directly related to the biological conditions that promote bingeing rather than secondary to antidepressant effects (Blouin et al., 1988). Consistent with this idea, no differences between groups on measures of depression were evident in the present study. Both the control and dexfenfluramine groups reduced their bulimic symptomatology during the first week and no differences between groups were evident on depression scores. This is similar to the results of Fahy et al. (1993). Blouin et al.

(1988) observed a decline in bulimic symptomatology and depression in the dl-fenfluramine group. The placebo group in that study did not show reduced bulimic behaviour nor did they experience a reduction in depression. From the results of the present study and that of Blouin et al. (1988), it would seem reasonable to infer that alleviation of depression accompanies behavioural control over bingeing and purging. Credence to this possibility is provided by the fact that fenfluramine did not reduce depressive symptomatology in unipolar depressives (Murphy, Slater, & de la Vega, 1984). It therefore seems unlikely that dexfenfluramine has direct antidepressant properties in bulimic patients. These results provide evidence that bulimia nervosa and depression are separate disorders.

As was found by Fahy et al. (1993), dexfenfluramine did not appear to have direct effects on specific eating disorder psychopathology or more general but characteristic disturbances. Both groups improved on psychiatric measures. From this it is inferred that attitudinal change appeared to be associated with changes in behavioural symptomatology.

It is noteworthy that the subjects in the active drug group tended to experience a rebound in depression, interoceptive awareness, hostility, alienation, feelings of guilt and a reduction in loss of appetite following termination of drug administration. One possibility is that the return of appetite occurred because of the cessation of

dexfenfluramine-induced feelings of satiety. While the return of negative psychological symptoms may also directly accrue from discontinuation of the drug, more likely they were brought on by increased difficulty in resisting binge behaviour because of the failure of satiety mechanisms. The active drug group's change in binge frequency was correlated with scores on the BDI at Week 2 and post-treatment. Considering the fact that groups did not differ on measures of depression, and the lack of evidence that dexfenfluramine has antidepressant properties, it would seem reasonable to suggest that the lowered levels of depression maintained during the second week of drug treatment, and the increase following drug cessation was linked to the enhanced and subsequently decreased feelings of control resulting from dexfenfluramine's influence on feelings of satiety.

Bulimics typically start each day with the resolve not to binge and purge. Their fear of weight gain prompts them to severely restrict their food intake during the day, resulting in extreme biological urges to eat. During the evening, in the privacy of their homes, they are unable to resist these biological urges and begin to eat. Ingestion of food is often rapid, and once having begun to eat the bulimic finds it difficult to stop. Anxiety over the food intake leads to purging. The bulimic individual views her response to the biological urge as impaired interoceptive awareness, lack of control, weakness and proof that she is a

failure. Feelings of guilt and lowered self-esteem contribute to depression, hostility, and a sense of alienation. It is reasonable to speculate that improvement of primary bulimic symptomatology during dexfenfluramine administration was accompanied by increased feelings of control and improved psychological status. Withdrawal of the satiety-inducing aid rendered this control more difficult, resulting in reduced perception of self-control, and a return of self-doubt and self-criticism.

It was hypothesized that dexfenfluramine would also reduce binge size as a result of increased feelings of satiety. The results of the present study do not support this hypothesis, however. This may be due to limitations in the sensitivity of the Daily Binge Record. Binge size was represented as calories per binge. The computation of calories per binge depended on the binge frequencies from the Daily Binge Record. Attempts were made to operationalize binges by time and quantity of food eaten, however the manner in which subjects record their food intake necessitates subjective interpretation on the part of the investigator. Added to this, bulimic patients are a heterogeneous group, and the variability of their behaviour is conveyed on the Daily Binge Records. As Blouin et al. (1988) found in their earlier research, it is often impossible for the investigator to determine the end of one binge, and the commencement of the next. The bulimic

individual may eat what they consider to be too much, become distressed and induce vomiting, and then be unable to refrain from eating again. This pattern of behaviour may continue over a period of time. Or a binge may be interrupted by a telephone call or the brief presence of a family member, and then reinstated. Are these multiple binges or one binge episode? The same limitation may also explain the lack of concordance between binge frequencies from the Daily Binge Record and the Weekly Bulimic Symptom Checklist where binge frequencies were determined by the subjects themselves.

If bingeing behaviour is an attempt to attain a particular desired state, attainment of that state may be the marker of the end of a binge for the bulimic individual. The behaviour elicited in response to the instruction by Kaye et al. (1988) to binge and vomit until a "desired effect" was attained is in keeping with this possibility. Only two of the six subjects who voluntarily stopped bingeing and purging stopped after one binge and vomit episode. Two subjects required two episodes and the other two required three to attain the desired effect. Thus, if bingeing is an attempt to attain a desired state, it may require more than one overeating and purging episode to attain that state.

When completing the Weekly Bulimic Symptom Checklist subjects may have been recording the frequency of satisfying their urges, which may require numerous "binges"

interspersed by vomiting, rather than enumerating each session of overeating. They may also have been taking into account the intensity of the urge to binge, the feelings of loss of control, the size of the binge. Their subjective perception at the end of the week may be more informative than daily recordings of food intake. The definition of abnormal eating relies substantially on the subjective report of the patient. The psychological feeling of being out of control is required by DSM-III-R but there is no standardized assessment of the size of a 'binge'.

Therefore, it would seem that binge frequencies reported by the subjects themselves are more appropriate measures than frequencies determined by someone else. The Daily Binge Record may be a less sensitive measure than the Weekly Bulimic Symptom Checklist. It may measure less of the construct of interest, more constructs of disinterest, and be subject to errors of measurement. The sensitivity of the weekly measure to the drug effects in the current study is consistent with the literature, which supports the interpretation that the daily measure is the less sensitive measure.

One major aim of this study was to explore the possibility that diet history would predict response to dexfenfluramine. Serotonin synthesis can be altered by tryptophan availability since tryptophan hydroxylase, the rate-limiting enzyme in the synthetic pathway, is

unsaturated with tryptophan under normal physiological conditions. Availability of a neurotransmitter can influence synaptic transmission, and consequently the function of the neurochemical pathway (Cooper et al., 1991). Delgado et al. (1989) showed that a tryptophan restricted diet led to decreased plasma tryptophan and blunted prolactin response to a subsequent L-Tryptophan infusion. Research has shown that dieting lowers plasma tryptophan, and subsequent challenge with intravenous tryptophan causes an enhanced prolactin response, indicating alteration in serotonergic function (Anderson et al., 1990). Since severe dieting is the most frequent antecedent of bingeing behaviour (Halmi, 1992), and research has shown that bulimic patients show lower tryptophan/LNAA ratios in response to test meals and blunted prolactin response to m-CPP, a serotonergic agonist, it was proposed that diet behaviour influenced serotonergic function in this population. If bulimic behaviour is related to decreased brain serotonin as a consequence of dieting, then perhaps manipulation of brain serotonin neurotransmission would reverse the adverse consequences. Following this line of reasoning, it was hypothesized that a history of severe dieting would predict response to dexfenfluramine. The low correlations of dietary history variables with change in bulimic behaviour variables and their inability to predict response to dexfenfluramine were unexpected.

The results of this study do not support the hypothesis that there is a direct link between dietary history, serotonin metabolism and failure in satiety. However, measures used to represent duration, severity and preferred methods of dieting were retrospective and subjective in a group that is known to have distorted cognitions toward eating. In addition, it is possible that factors that were not measured such as rate of weight loss or other similar elements of diet history would be more relevant. It would seem reasonable to conclude that dieting plays some role in the etiology of bulimia nervosa since dieting is the most common precipitant to bulimia, it is more common among women than men, and bulimia is predominantly a female disorder. Although not all women who diet develop bulimia, it may be that dieting is a behaviour which puts certain individuals at risk for developing eating disorders.

The substantial reduction in primary bulimic symptomatology in the placebo group observed in this study has been observed in previous pharmacotherapy research with this population (Agras et al., 1987; Fahy, et al., 1993; FNBC Study Group, 1992; Kennedy et al., 1993; Mitchell & Groat, 1984; Sabine, et al. 1983; Walsh et al., 1987). This reduction may be spontaneous remission, placebo effect, or may be the result of self-monitoring. It should be noted that self-monitoring is a commonly used behaviour change procedure and self-monitoring may have been therapeutic for

the control group. The sample used in this study were patients of an eating disorders clinic and as Mitchell & Groat (1984) point out, patients who have made the decision to seek help may have a high degree of motivation. Sabine et al. (1983) suggest that even the regular contact for assessment with someone interested in their condition, while in no way approaching psychotherapy, may be therapeutic for this group. The continued reduction in primary bulimic symptomatology in both groups seen at the post-treatment measure in this study may have been response to this therapeutic contact.

Mitchell et al. (1988) found that intensive behaviour therapy was superior to imipramine in treating bulimia nervosa, imipramine was superior to placebo, but the combination of psychotherapy and pharmacotherapy was not more effective than psychotherapy and placebo. This evidence of a ceiling effect, and the reduction in bulimic behaviour in the placebo group seen in this study, lend support to the suggestion of Fahy et al. (1993) that the effect of dexfenfluramine was submerged in the powerful effects of cognitive-behavioural therapy provided in their study.

It is worth noting that the only group difference on the psychiatric measures was on measurement of somatization, and that difference was evident even at baseline. The dexfenfluramine group was significantly more concerned with

their physical state than the placebo group. Both groups improved on this measure. The reduction of somatization of the active drug group, despite their sensitivity to bodily sensations, is consistent with the few side effects reported while taking dexfenfluramine. The only significant side effect was fatigue which was elevated at Week 1 and gone by Week 2.

The absence of unpleasant side effects and the short duration of this study, resulted in a very low drop-out rate (6%). This is a very important consideration in clinical studies. Unlike laboratory studies, where the researcher can exert control over influences not being studied and detect small effects of experimental manipulation, clinical studies must rely on sample size to detect sometimes small, but meaningful effects. Using the difference between groups in binge change at Week 1, and the sample size of 80 subjects, power was calculated to be .86 in this study. The low drop-out rate also contributes to the generalizability of the results because of minimal self-selection of the study sample.

Although subjects were assigned randomly, the dexfenfluramine group reported more frequent bingeing and purging at baseline. Consequently although the dexfenfluramine group significantly reduced their bulimic behaviour during the first week of drug administration and the placebo group did not, groups were not significantly

different at the Week 1 assessment. Conversion of the bulimic symptomatology frequency scores to difference scores allowed us to compare the groups in a more meaningful way. However, this pre-treatment difference raises the question of whether the effect of dexfenfluramine would generalize to less severe symptomatology.

This research contributes to the effort to determine what biological contributions there may be to bulimia nervosa and to the identification of etiological factors. Administration of dexfenfluramine resulted in swift reductions in bulimic symptomatology. From this we may conclude that manipulating serotonin with a specific serotonergic agonist reduces bulimic symptomatology without non-specific manipulation (i.e. antidepressant effect). The effectiveness of a specific serotonergic agonist in reducing bulimic symptomatology provides evidence that the serotonergic pathway is involved in this disorder. Dexfenfluramine's known food-intake reducing properties, and enhanced satiety ratings seen in previous research in a bulimic population (Robinson et al., 1985) suggest that its effectiveness in reducing binge frequency lies in its ability to enhance feelings of satiety. These observations are consistent with suggestions in the literature that it may be that biological conditions that result in impairment in the mechanisms of satiety promote bulimia.

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Appendix I

Description of Tests and Standardized Interviews

1. Diagnostic Schedule of Eating Disorders (DSED).

The DSED (Johnson, 1985) is a self-report questionnaire which provides information on demographics, weight history, body image dieting history, binge and purge behaviours, exercise habits, sexual functioning, menstruation, medical and psychiatric history, family history, and life adjustment.

2. National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS).

The NIMH-DIS (Robins, Helzer, & Ratcliffe, et. al, 1981) is a structured diagnostic interview which provides Axis I DSM-III diagnoses. A computerized version of this interview, modified to address DSM-III-R criteria, the C-DIS-R (Blouin, Perez, & Blouin, 1988), was employed in the present study.

3. Eating Disorder Inventory (EDI)

The EDI (Garner, Olmstead, & Polivy, 1983) is a self-report questionnaire measuring drive for thinness, urge to binge, body dissatisfaction, perfectionism, interoceptive awareness, interpersonal distrust, maturity fears and ineffectiveness.

4. Hopkins 90-item Symptom Checklist-Revised (SCL-90-R)

The SCL-90-R (Derogatis, L. R., 1977) is a self-report symptom inventory assessing somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.

5. Beck Depression Inventory (BDI)

The BDI (Beck, Ward & Mendelson, 1961) is a self-report inventory of cognitive and neurovegetative symptoms of depression.

6. Daily Hassles Scale (DHS) and Daily Uplift Scale (DUS)

The DHS (Kanner, Coyne, Schaefer & Lazarus, 1981) is a list of 117 minor problematic life events to be rated on a three-point scale from somewhat to extremely severe. The DUS consists of a list of 135 positive events .

7. The Social Readjustment Rating Scale (SRRS)

The SRRS (Holmes & Rahe, 1967) is a measure of major life stressors.

8. State Trait Anxiety Inventory (STAI)

The STAI (Spielberger, 1983) evaluates both acute and chronic feelings associated with anxiety.

9. Profile of Mood States (POMS)

The POMS (McNair, Lorr & Doppleman, 1971) is a self-report mood scale which yields six factors: tension-anxiety, depression, anger-hostility, vigour, fatigue and bewilderment.

The Binge Food Record

Please rate the likelihood that you would binge on the following foods by circling your choice from the options given.

1. Bread/ Cereal/ Popcorn

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

2. Pasta

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

3. Cheese/ White milk/ Plain Yoghurt

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

**4. Flavoured yoghurt/
Chocolate milk/ Ice cream**

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

5. Fruit/ Vegetables

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

6. Meat/ Fish/ Poultry/ Eggs

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

7. Sweets (cakes, pies, candy, chocolate bars, etc.)

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

8. Peanuts/ Other nuts

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

9. Salty snack foods (chips, cheesies, etc., but not including pork rinds or Baco-O-Bits which are coded under meat)

1. Always
2. Frequently
3. Sometimes
4. Rarely
5. Never

WEEKLY SYMPTOM CHECKLIST

ID # _____ Date _____

1. Please indicate the number of episodes or times in the past week you experienced the following symptoms:

<u>Symptom</u>	<u>Number of episodes last week</u>
a) Binging	_____
b) Vomiting	_____
c) Purging (laxative and/or diuretic use)	_____

2. Please rate the severity of the following symptoms using the corresponding rating scale. The rating of severity should correspond to the degree to which these symptoms have been a problem for you (regardless of frequency) in the past week. Circle your choice for each item.

<u>SYMPTOM</u>	<u>LEVEL OF SEVERITY</u>
1. Binge eating	a) Not at all b) A little c) Moderately d) Quite a bit e) Extremely
2. Vomiting	a) Not at all b) A little c) Moderately d) Quite a bit e) Extremely
3. Other purging (i.e., laxative and/or diuretic use, etc.)	a) Not at all b) A little c) Moderately d) Quite a bit e) Extremely
4. Pre-occupation with food	a) Not at all b) A little c) Moderately d) Quite a bit e) Extremely
5. Lack of control over eating	a) Not at all b) A little c) Moderately d) Quite a bit e) Extremely
6. Overall severity of these symptoms	a) Not at all b) A little c) Moderately d) Quite a bit e) Extremely

D.S.E.D.

DIAGNOSTIC SURVEY FOR EATING DISORDERS

INSTRUCTIONS:

This questionnaire covers several eating problems that may or may not apply to you. You may find it difficult to answer some questions if your eating pattern is irregular or has changed recently. Please read each question carefully and choose the answer that best describes your situation most of the time. Also, please feel free to write remarks in the margins if this will clarify your answer. Thank you.

NAME: _____

DATE: _____

CURRENT TELEPHONE NUMBER: (W) _____ (H) _____

IDENTIFYING AND DEMOGRAPHIC INFORMATIONSex: ☐ Male ☐ Female Age: _____Race: ☐ White ☐ Black Other (Specify) _____

Your present religious affiliation:

☐ Protestant ☐ Catholic ☐ Jewish ☐ No affiliation ☐ Other (Specify) _____

Religious affiliation of your family of origin:

☐ Protestant ☐ Catholic ☐ Jewish ☐ No affiliation ☐ Other (Specify) _____

Marital Status:

☐ Presently in first marriage ☐ Widowed and presently remarried

☐ Divorced and presently remarried ☐ Widowed and not presently remarried

☐ Divorced or separated and not presently married ☐ Never married

What is your present primary role?

☐ Wage earner ☐ Housewife ☐ Student ☐ Other (Specify) _____

Highest Occupational level attained

Check one for each person

	Self	Father	Mother	Spouse
Higher executive, proprietor of large concern, major professional	☐	☐	☐	☐
Business manager of large concern, proprietor of medium-sized business, lesser professional	☐	☐	☐	☐
Administrative personnel, owner of small independent business, minor professional, owner of large farm	☐	☐	☐	☐
Clerical or sales worker, technician, owner of little business, owner of medium-sized farm	☐	☐	☐	☐
Skilled manual employee, owner of small business	☐	☐	☐	☐
Machine operator, semiskilled employee, tenant farmer who owns little equipment	☐	☐	☐	☐
Unskilled employee, sharecropper	☐	☐	☐	☐
Does not apply (Never worked in paid employment)	☐	☐	☐	☐
Does not apply (No spouse)	☐	☐	☐	☐
Information not available	☐	☐	☐	☐

Current living arrangement:

- ☐ With parents or relatives ☐ Dorm or shared apartment with friend
- ☐ Conjugal (intimate relationship with other person, including spouse, boyfriend, etc.)
- ☐ Alone

Highest level of education

Check one for each person

	Self	Father	Mother	Spouse
Completed post-graduate training	☐	☐	☐	☐
Some post-graduate training	☐	☐	☐	☐
Completed college, receive four year academic degree	☐	☐	☐	☐
Completed high school, may have attended or completed trade school or non-academic training requiring high school completion	☐	☐	☐	☐
Attended high school	☐	☐	☐	☐
Completed grammar school (8th grade)	☐	☐	☐	☐
Attended grammar school	☐	☐	☐	☐
No schooling	☐	☐	☐	☐
Does not apply (No spouse)	☐	☐	☐	☐
Information not available (Specify why)	☐	☐	☐	☐
Please describe your current occupation				

WEIGHT HISTORY

Current weight _____ lbs.

Current height _____ inches

Desired weight _____ lbs.

Adult Years

Highest adult weight since age 18 _____ lbs. at age _____

Lowest adult weight since age 18 _____ lbs. at age _____

How long did you remain at your lowest adult weight? _____ days

_____ months

_____ years

Adolescent Years

Highest weight between ages 12-18 _____ lbs. at age _____

Lowest weight between 12-18 _____ lbs. at age _____

Childhood

How did you perceive your weight as a child between the ages 6 - 12 years old?

As a child were you teased about your weight?

☐ Yes about being underweight☐ Yes about being overweight

To what extent were you teased?

At your current weight do you feel that you are:

Has there ever been a time when your feelings about yourself or your social life have changed substantially as a result of losing weight?

☐ Yes☐ No

Please explain _____

How dissatisfied are you with the way your body is proportioned?

Please indicate on the scales below how you feel about the different areas of your body:

	<i>Strongly positive</i>	<i>Moderately positive</i>	<i>Neutral</i>	<i>Moderately negative</i>	<i>Strongly negative</i>
Face	☐	☐	☐	☐	☐
Arms	☐	☐	☐	☐	☐
Shoulders	☐	☐	☐	☐	☐
Breasts	☐	☐	☐	☐	☐
Stomach	☐	☐	☐	☐	☐
Buttocks	☐	☐	☐	☐	☐
Thighs	☐	☐	☐	☐	☐

How fat do you feel?

<i>Extremely Fat</i> 4	<i>Very Fat</i> 3	<i>Fat</i> 2	<i>Somewhat Fat</i> 1	<i>Not at all Fat</i> 0

How often do you weigh or measure your body size?

☐ <i>More than daily</i>	☐ <i>Weekly</i>
☐ <i>Daily</i>	☐ <i>Monthly</i>
☐ <i>More than weekly</i>	☐ <i>Less than monthly</i>

DIETING BEHAVIOR

Have you ever been on a diet? ☐ *Yes* ☐ *No*

At what age did you begin to restrict your food intake due to concern over your body size?

_____ *years old*

In your first year of dieting, how many time did you start a diet? *No. of times* _____

Over the last year, how often have you begun a diet? *No. of times* _____

Please rank from 1 - 9 your preferred way of dieting (1 = most preferred, 9 = least preferred)

<i>Skip meals</i>	_____	<i>Reduce portions</i>	_____
<i>Completely fast</i>	_____	<i>Go on fad diets</i>	_____
<i>Restrict carbohydrates</i>	_____	<i>Reduce calories</i>	_____
<i>Restrict sweets</i>	_____	<i>Other (specify)</i>	_____
<i>Restrict fats</i>	_____		

If you have ever been encouraged to diet, please rank from 1 - 10 the people that encouraged you to diet the most (1 = most encouraged, 10 = least encouraged)

Boyfriends _____
 Girlfriends _____
 Mother _____
 Father _____
 Brother _____

Sister _____
 Employer _____
 Teacher/Coach _____
 Other relative _____
 Other (Please specify) _____

BINGE EATING BEHAVIOR

Have you ever had an episode of eating a large amount of food in a short space of time (an eating binge)

☐ Yes

☐ No

Please circle on the scales below, how characteristic the following symptoms are of your binge eating

Never 0 Rarely 1 Sometimes 2 Other 3 Always 4

I consume a large amount of food during a binge

I eat very rapidly

I feel out of control when I eat

I feel miserable or annoyed after a binge

I got uncontrollable urges to eat and eat until I feel physically ill

I binge eat in private

How long does a binge usually last?

☐ Less than one hour

☐ 1-2 hours

☐ More than 2 hours

Please rank 1 - 9 the times of day that you are most likely to binge (1 = most likely, 9 = least likely)

8 am - 10 am _____

6 pm - 8 pm _____

10 am - 12 pm _____

8 pm - 10 pm _____

12 pm - 2 pm _____

10 pm - 12 am _____

2 pm - 4 pm _____

After midnight _____

4 pm - 6 pm _____

Please rank from 1 - 6 the places where you are most likely to binge (1 = most likely, 6 = least likely)

Home _____

Work _____

Restaurant _____

Car _____

Party _____

Other (Specify) _____

Please rank from 1 - 5 how likely you are to binge eat in the presence of the following people
(1 = most likely, 5 = least likely)

Friends _____

Parents _____

Alone _____

Spouse/Significant other _____

Children _____

How old were you when you began binge eating?

_____ years old

How long have you had a problem with binge eating?

_____ days

_____ months

_____ years

Within the last month, what has been your average number of binge episodes per week?

_____ binges

What is the longest period you have had without binge eating since the onset of the problem?

_____ days

_____ months

_____ years

What were the circumstances that helped you to not binge eat for that period of time (if more than one event is applicable, please rank order the importance of the event with 1 = most important)

Began dieting _____

Left home _____

Started exercising _____

Divorce _____

Sought professional help _____

Marriage _____

Began romantic relationship _____

Pregnancy _____

Left romantic relationship _____

Work _____

Developed illness _____

Vacation _____

Other (Specify) _____

Please rank from 1 - 7 the foods that you are most likely to binge on (1 = most likely, 7 = least likely)

Bread/cereal/pasta _____

Salty snack foods _____

Cheese/milk/yogurt _____

Sweets _____

Please rank from 1 - 7 the foods that you are most likely to binge on (1 = most likely, 7 = least likely) (con't)

<i>Fruit</i>	_____	<i>Vegetables</i>	_____
<i>Meat/fish/poultry/eggs</i>	_____		

Please rank from 1 - 7 the foods that you are most likely to eat when you are not bingeing
(1 = most likely, 7 = least likely)

<i>Bread/cereal/pasta</i>	_____	<i>Salty snack foods</i>	_____
<i>Cheese/milk/yogurt</i>	_____	<i>Sweets</i>	_____
<i>Fruit</i>	_____	<i>Vegetables</i>	_____
<i>Meat/fish/poultry/eggs</i>	_____		

Were there any particular events in your life, either positive or negative, which preceded or coincided with the onset of your eating problems? (Check as many as applicable)

<i>Death of significant other</i>	_____
<i>Leaving home</i>	_____
<i>Illness or injury to self</i>	_____
<i>Failure at school or work</i>	_____
<i>Difficult sexual experience</i>	_____
<i>Illness or injury to family member or significant other</i>	_____
<i>Problems in romantic relationship</i>	_____
<i>Family problems</i>	_____
<i>Teasing about appearance</i>	_____
<i>Prolonged period of dieting</i>	_____
<i>Marriage</i>	_____
<i>Pregnancy</i>	_____
<i>Work transition</i>	_____

Other, Please specify _____

Using the scale below, please select the number which indicates the intensity of each of the following feelings before a binge:

<i>Extremely intense 4</i>	<i>Very intense 3</i>	<i>Moderately intense 2</i>	<i>Slightly intense 1</i>	<i>Not at all intense 0</i>
<i>Calm</i>	_____	<i>Bored</i>	_____	
<i>Empty</i>	_____	<i>Frustrated</i>	_____	
<i>Confused</i>	_____	<i>Panicked</i>	_____	
<i>Excited</i>	_____	<i>Relieved</i>	_____	
<i>Angry</i>	_____	<i>Guilty</i>	_____	
<i>Spaced out</i>	_____	<i>Depressed</i>	_____	
<i>Inadequate</i>	_____	<i>Nervous</i>	_____	
<i>Disgusted</i>	_____	<i>Lonely</i>	_____	

Other (Please specify) _____

Have you noticed a relationship between the frequency of your binge eating and your menstrual cycle?

☐ Yes

☐ No

If yes, please indicate when during your cycle you feel most vulnerable to binge eating.

☐ During menstruation

☐ 11-14 prior to menstruation

☐ 7-10 days prior to menstruation

☐ 3-8 days prior to menstruation

☐ 1-2 days prior to menstruation

☐ After menstruation

How uncomfortable are you with your binge eating behavior?

*Extremely
uncomfortable*

4

*Very
uncomfortable*

3

*Uncomfortable
uncomfortable*

2

*Somewhat
uncomfortable*

1

Not at all

0

How willing would you be to gain 10 pounds in exchange for not binge eating any more?

*Extremely
willing*

4

*Very
willing*

3

*Willing
willing*

2

*Somewhat
willing*

1

*Not at all
willing*

0

PURGING BEHAVIOR

Have you ever vomited or spit out food after eating in order to get rid of the food eaten?

☐ Yes

☐ No

How old were you when you induced vomiting for the first time?

_____ years

How long have you been using self-induced vomiting?

_____ days

_____ months

_____ years

Have you ever used laxatives to control your weight or "get rid of food"?

☐ Yes

☐ No

How old were you when you first took laxatives for weight control?

_____ years

days months years

<i>Never</i>	_____	<i>Several meals a week</i>	_____
<i>Less than 1 meal a week</i>	_____	<i>One meal a day</i>	_____
<i>About one meal a week</i>	_____	<i>More than one meal a day</i>	_____

☐ 1 - 15 minutes ☐ 16 - 30 minutes ☐ 31 - 45 minutes ☐ 46 - 60 minutes ☐ One hour or longer

- ☐ *"Binge eating" came first*
- ☐ *Neither came first, I have only "binge eating" episodes*
- ☐ *Vomiting came first*
- ☐ *Neither came first, I have only vomiting episodes*
- ☐ *Both occurred at the same time*
- ☐ *Neither came first, I have never had "binge eating" or vomiting episodes*

[illegible]

Using the scale below, please select the number which indicates the intensity of each of the following feelings state before a purge.

<i>Extremely intense 4</i>	<i>Very intense 3</i>	<i>Intense intense 2</i>	<i>Slightly intense 1</i>	<i>Not at all intense 0</i>
<hr/>				
<i>Calm</i>	_____	<i>Bored</i>	_____	
<i>Empty</i>	_____	<i>Frustrated</i>	_____	
<i>Confused</i>	_____	<i>Panicked</i>	_____	
<i>Excited</i>	_____	<i>Relieved</i>	_____	
<i>Angry</i>	_____	<i>Guilty</i>	_____	
<i>Spaced out</i>	_____	<i>Depressed</i>	_____	
<i>Inadequate</i>	_____	<i>Nervous</i>	_____	
<i>Disgusted</i>	_____	<i>Lonely</i>	_____	
<i>Other (Please specify)</i> _____				

Using the scale above, please select the number which indicates the intensity of each of the following feelings state after a purge.

<i>Calm</i>	_____	<i>Bored</i>	_____
<i>Empty</i>	_____	<i>Frustrated</i>	_____
<i>Confused</i>	_____	<i>Panicked</i>	_____
<i>Excited</i>	_____	<i>Relieved</i>	_____
<i>Angry</i>	_____	<i>Guilty</i>	_____
<i>Spaced out</i>	_____	<i>Depressed</i>	_____
<i>Inadequate</i>	_____	<i>Nervous</i>	_____
<i>Disgusted</i>	_____	<i>Lonely</i>	_____
<i>Other (Please specify)</i> _____			

EXERCISE

How many minutes a day do you currently exercise (including going on walks, riding bicycle, etc.)?

_____ Minutes

Have you ever competed in any of the following physical activities? (*Check as many as are applicable*)

<i>Distance running</i>	_____
<i>Weight lifting</i>	_____
<i>Dancing</i>	_____
<i>Gymnastics</i>	_____
<i>Wrestling</i>	_____
<i>Tennis</i>	_____
<i>Swimming</i>	_____

Other (Please specify) _____

OTHER BEHAVIOUR

Do you feel that you have ever had an alcohol or drug abuse problem? (Circle one)

When did the drug or alcohol problem start in relationship to the eating problem?

I never had a drug or alcohol problem _____

Before the eating problem began _____

After the eating problem began _____

At the same time the eating problem began _____

Please indicate how frequently you have used the following substances since the onset of your eating problem.

ALCOHOL (SPECIFY TYPE)	AMOUNT	DAILY	WEEKLY	MONTHLY	LESS THAN MONTHLY
Amphetamines (uppers)					
Barbiturates (downers)					
Hallucinogens					
Marijuana					
Tranquilizers					
Cocaine					
Cigarettes	☐ None ☐ 1 - 1½ packs/day ☐ 1 pack/day ☐ More than 1 pack/day				

Have you ever made a suicide attempt?

☐ Yes

☐ No

Describe: _____

Have you ever tried to physically hurt yourself (i.e. cut yourself, hit yourself with intent to hurt, burn yourself with cigarettes)?

☐ Yes

☐ No

Describe: _____

MENSTRUAL HISTORY

Age at onset of menses (if you have never gotten your period please mark "0")

_____ *years*

Since the onset of your eating problems, how many times have you stopped menstruating for three months or more (which were unrelated to pregnancy)?

_____ *number of times*

Before the onset of your eating problems, how many times had you stopped menstruating for three months or more (which was not related to pregnancy)?

_____ *number of times*

Since the onset of your eating problems, what is the total number of months that you have not menstruated (months unrelated to pregnancy)?

_____ *months*

Before the onset of your eating problems, what is the total number of months that you did not menstruate (months unrelated to pregnancy)?

_____ *months*

Approximate regularity of cycles before onset of eating difficulties (*Check one*)

Fairly regular (same number days + 3)

Somewhat irregular (variation 4 - 10 days)

Very irregular (variation greater than 10 days)

Never menstruated

How many times in the past have you had episodes of loss of menstrual periods lasting 3 months or more associated with significant weight loss when you were not "binge eating" or pregnant?

_____ *number of times*

END

0 3-0 6-9/6

FIN