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ABSTRACT

This paper reviews the literature on the physiological causes of bulimia and investigates the rationale behind the usage of antidepressant medication in the treatment of bulimia nervosa. No definite conclusions can be stated regarding the physiology of bulimia, but a number of hypotheses are suggested. It appears that the hypothalamus is involved in bulimia nervosa, and that endorphins related to obesity are also apparent. The literature further hypothesizes that the satiety function is impaired in bulimics, and that serotonin and norepinephrine levels are also impaired. The treatment of bulimia nervosa with tricyclic antidepressants remains controversial. These drugs work with many people, but the reasons why they work remain somewhat unclear. One hypothesis states that major depression may be associated with a lack of activity of norepinephrine in the brain, and that serotonin may also be involved in major depression. Both of these neurotransmitters have been implicated as being dysfunctional in bulimics, leading to the hypothesis that bulimia and mood disorders are somehow related. Chemotherapy as an effective treatment modality for bulimia should remain under investigation. It is hypothesized that desipramine will be effective in reducing the bingeing and purging behaviors of bulimics, and that an adequate blood level needs to be reached before desipramine produces its desired effects. If this hypothesis proves to be valid, it will add to the support that chemotherapy is a viable treatment option for bulimia, that bulimia may somehow be linked with affective disorder, and that bulimia may have a physiological basis. (LLL)

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Physiological Bases of Bulimia, and Antidepressant Treatment

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Abstract

Bulimia nervosa is one of the major health problems in the United States, especially in young people of high school and college age. This paper reviews the literature on the physiological causes of bulimia and investigates the rationale behind the usage of antidepressant medication in the treatment of bulimia nervosa. It also discusses the connection between bulimia nervosa and affective disorders. Endorphins and the hypothalamus, among other mechanisms, are hypothesized in having a role in the cause of bulimia nervosa.

Bulimia and anorexia nervosa are major health problems in the United States, especially in high schools, universities and colleges (Mitchell & Eckert, 1987). According to Mitchell and Eckert (1987), published studies on the prevalence of bulimia in women list between 26% to 79% of these women as reporting binge eating, depending upon the study's definition of bulimia. Mintz and Betz (1988), however, note that bulimia does not appear to be as prevalent on college campuses as many researchers believe. They found that only 3% of the subjects in their study could be classified as being bulimic; however, only 33% of their subjects reported normal eating habits. Regardless, bulimia is clearly a problem no matter whose definition is used.

Fortunately, advances in chemotherapy in recent years, particularly in the area of antidepressant medications, have increased the efficacy of the treatment of bulimics. Psychotherapy with eating disordered clients has never been easy, perhaps due to a lack of client motivation more than anything else (Mitchell & Eckert, 1987; Walsh, Glaúis, Roose, Stewart, Stetner & Glassman, 1988). Thus, chemotherapy would seem to be a sensible alternative, as it requires less motivation than psychotherapy and, in a sense, can be more cost-effective.

What, exactly, causes bulimia and what are some of the physiological mechanisms that underlie bulimia? Gandour (1984) and Herzog (1986) both note that bulimia may be caused by a hypothalamic dysfunction. However, studies that have examined electroencephalograms (EEG's) of bulimic individuals have not supported this hypothesis. Gandour (1984) concludes that the notion of a dysfunctional hypothalamus in bulimics should remain at the hypothetical stage. However, Kaplan and Woodside (1987) state that the hypothalamic-pituitary function is indeed disturbed in people who have anorexia nervosa or bulimia (or a combination of the two). These disturbances are generally mediated by mechanisms that are secondary to the effects of disordered eating. Abnormalities in thermoregulation, for example, and in gonadotropic hormone levels relate directly to weight loss and are seen in other states of emaciation regardless of the cause. Some other abnormalities like amenorrhea may reflect the effects of weight loss, disordered eating or other factors that are not known. Kaplan and Woodside (1987) conclude that biology helps to perpetuate eating disorders. However, they caution that little remains known about the possible biological contributions to the predisposition or precipitation of eating disorders.

Mitchell and Eckert (1987) note that in animal studies norepinephrine, when released into the hypothalamus, stimulates the animals to eat even if the animal is sated from previous exposure to food. The desire to ingest carbohydrates is also increased. Serotonin produces the opposite effect and decreases the desire to ingest carbohydrates. Mitchell and Eckert (1987) note that these two neurotransmitters may be involved with eating disorders. For example, they state that serotonin dysfunction and disregulation may occur in bulimics, thus leading to the disinhibition of carbohydrate intake. Therefore, these symptoms may be manifested by the binging of high carbohydrate foods, one of the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders--Third Edition (American Psychiatric Association, 1980). Davis, Freeman and Garner (1988) also discovered that bulimics tend to binge more on grains and cereals during a binge episode.

Kaplan and Woodside (1987) also support Mitchell and Eckert's (1987) view that neurotransmitters are directly implicated in the control of feeding behavior, especially in the animal literature. Serotonin inhibits feeding by inducing satiety, while norepinephrine stimulates feeding through its activity in the medial hypothalamus and paraventricular nucleus and inhibits feeding through its actions on the lateral hypothalamus. These neurotransmitters may be affected by the availability of certain nutrients; for example, serotonin may

be regulated by the availability of tryptophan. Kaplan and Woodside (1987) also note that serotonin may be involved in the regulation of mood, pain, sleep, appetite, and in the control of some hypothalamic and pituitary hormones. The key here is that all of these functions have been found to be disturbed in people with eating disorders.

Johnson and Brief (1983) speak about the role of EEG abnormalities in bulimics and state that bulimia may be related to epileptic-style seizures. The relation between seizure disorders and bulimia may be related to a hypothalamic dysfunction or to an unknown dysfunction that increases the person's arousal state. They also discuss the role of endogenous opiates (endorphins) and state that the role endorphins play in causing obesity may contribute to the knowledge of bulimia's causes.

The hypothesized involvement of endorphins in the causes of bulimia is espoused by Mitchell, Laine, Morley and Levine (1986). Endorphins are proteins that may act as neurotransmitters and are structurally similar to opiates. Endorphins have been linked to pain control, addictive behaviors and to the control of eating. Endorphin levels were found to be elevated in genetically obese rats (Margules, Moisset, Lewis, Shibuya, & Pert, 1978). In satiated rats, endorphins injected into the ventromedial hypothalamus were found to stimulate food intake (Grandison & Guidotti, 1977). Naloxone (a

narcotic antagonist) has been shown to stop the overeating of genetically obese rats (Holtzman, 1974) and to cause weight loss and appetite loss when given to humans (Hollister, Johnson, Bookhabzer & Gillespie, 1981).

Mitchell et al. (1986) performed a trial of naloxone in bulimics. They were examining the hypothesis that elevated endorphin levels exist in some obese people; therefore, feeding would be suppressed using narcotic antagonists. Presumably these would antagonize the endogenous opioids as they antagonize exogenous narcotics such as morphine (Kyriakides, Silverston, Jeffcoate & Laurence, 1980; Morley & Levine, 1980). Mitchell et al. (1986), in their double-blind study, found that naloxone significantly suppressed food intake during binge episodes in hospitalized bulimics. Jonas and Gold (1986) also supported this result, but their experiment was an open label trial. Thus, more double-blind, placebo-controlled trials of naloxone should be performed on bulimics.

It thus seems that a hypothalamic dysfunction of some sort is involved in bulimia, but what that dysfunction is, and the nature of its involvement, is not yet clear. It can be hypothesized that serotonin and norepinephrine have an involvement with the feeding-satiety process and, for whatever reason, that process is dysfunctional in people who manifest bulimia and other eating disorders. It can also be hypothesized that serotonin and norepinephrine have

some involvement with bulimia and that this involvement involves the hypothalamus. There is literature to support this view yet it still remains unsubstantiated.

Menstrual abnormalities also occur in bulimics who are classified as normal weight; as many as one-third of bulimic patients may have extremely erratic menstruation (Fairburn & Cooper, 1984). Fairburn and Cooper (1984) note that the cause for this is not clear. Irregular eating patterns may somehow alter neurotransmitter levels in some way to change the release of hypothalamic hormones. It is also possible that these people are below their biologically determined set point for weight and thus have borderline levels of body fat.

Musisi and Garfinkel (1985) report that cortisol secretion may be disturbed in bulimics and that in normal weight bulimics, abnormal results occurred on the dexamethasone suppression test (DST). The DST's major purpose is to test an individual for endogenous depression. These DST results may be related to abnormal eating patterns or to a biologically underweight state even though normal weight is maintained. As a point of comparison, abnormal DST results may be related to weight loss and have been seen in nondepressed patients who had lost weight for other reasons (Fichter, Pirke & Holsboer, 1986).

The hormone cholecystokinin, located in the brain and in the gut, has been found to be involved in satiety regulation in rats, sheep, monkeys, and in humans (Bennett & McMartin, 1979; Geracioti & Liddle, 1988). Gut motility often seems to be impaired in bulimics (Kaplan & Woodside, 1987) and they tend to evidence clinical symptoms such as dyspepsia and early satiety. Geracioti and Liddle (1988) found that cholecystokinin was significantly impaired in bulimic patients. They conclude that bulimics do not have normal satiety and that they also have impaired secretion of cholecystokinin in response to a meal. A key suggestion they make is that both of these abnormalities may be improved by tricyclic antidepressants (a class of antidepressant agents), although the mechanism by which they may augment cholecystokinin secretion is unknown.

Mira, Stewart, Vizzard and Abraham (1987) found that women with an eating disorder (anorexia nervosa, bulimia or unclassified) had significantly higher cholesterol levels than their control group and significantly lower levels of potassium in their plasma. More importantly, decreased plasma potassium was found more commonly in those women who induced vomiting or abused laxatives, common occurrences among bulimics. Large amounts of potassium are lost through the gastrointestinal tract in people who vomit or purge as a

means of controlling weight. Measuring potassium levels might be useful as a diagnostic criterion for bulimia.

Bulimics also evidenced an elevated plasma cholesterol but this was more common in the patients with anorexia whom they studied. Mira et al. (1987) were unsure as to why cholesterol was elevated in subjects with eating disorders but they hypothesize that it may be due to impaired clearance of Low Density Lipid (LDL) cholesterol. Regardless of the reasons, this elevated plasma cholesterol places the eating disordered patient at an increased risk of cardiovascular disease (Mira et al., 1987). It has also been hypothesized that elevated cholesterol levels in bulimics may be a genetic marker but this has yet to be substantiated (Weninger & Getzfeld, 1990, in press).

What can be concluded regarding the physiology of bulimia? As the literature demonstrates, no definite conclusions can be stated. However, a number of hypotheses are suggested. It seems that the hypothalamus is involved in bulimia nervosa as many studies have stated. It is also possible that endorphins, related to obesity, may also be connected to bulimia. More importantly, the literature hypothesizes that the satiety function is impaired in bulimics and that serotonin and norepinephrine levels are also impaired. Included in this hypothesis is the notion that cholecystokinin levels are also impaired (Geracioti & Liddle, 1988). One can hypothesize, based upon the

evidence in the literature, that bulimia nervosa may be, in part, a biological disorder and may be related to satiety dysfunctions.

Geracioti and Liddle (1988) raise a key point when they suggest treating bulimia nervosa with tricyclic antidepressants. This is not a new concept but it remains controversial for many reasons, not the least of which is that the front-line usage of these drugs is for depression, not for treating bulimia. It is more helpful to examine how these drugs work and where they act in the body.

As stated previously, the tricyclics are a class of drugs in the category of antidepressant agents. As with most of the drugs used to treat psychiatric problems, their mechanisms of action are not completely understood (Baldessarini, 1985). The literature poses several hypotheses about how these drugs may work.

Baldessarini (1985) states that the tricyclics have acute sedative effects in animals and in humans. Most antidepressant agents have the ability to reverse or modify the sedation produced by reserpine. In addition, the tricyclics enhance the actions of norepinephrine and may block the effects of tyramine. These observations have led to the support of the amine hypothesis of affective disorders. This hypothesis suggests that major depression is associated with a relative lack of activity of certain amine neurotransmitters

in the brain, most probably norepinephrine, while mania may be associated with an overabundance of norepinephrine or of dopamine. Other amines such as acetylcholine and serotonin may also be involved in major depression.

Baldessarini (1985) says that a large part of the problem in understanding how antidepressants work is the lack of knowledge of the causes of the major affective (mood) disorders. Much research has been done but the research has not sufficiently proven a cause-effect relationship between physiological changes and depression. For example, many biological changes that occur in major mood disorders tend to return to normal once the mood disorder is in remission. These metabolic and physiological changes found in people who have major depression may be secondary to, or concomitant with, depression; they are not necessarily a cause of depression or an indication of a biological vulnerability to it. Baldessarini (1985) concludes by stating that no single biochemical nor neurophysiological hypothesis can account for the actions of all antidepressants.

Thus, these drugs work with many people, but the reasons why they work remain somewhat unclear. Baldessarini (1985) raises an important point in his discussion. He states that major depression may be associated with a lack of activity of norepinephrine in the brain, and that serotonin may also be involved in major depression. Both of these neurotransmitters have been

implicated as being dysfunctional in bulimics and therefore have been hypothesized as being related to bulimia (Kaplan & Woodside, 1987; Mitchell & Eckert, 1987).

This leads to an interesting hypothesis; that is, that bulimia and mood disorders are somehow related. Hudson, Pope and Jones (1983) hypothesize that, after reviewing biological tests and family histories, bulimia seems to be related to major affective disorder. Depressive symptoms were significantly reduced in the bulimic group being tested with imipramine, a tricyclic antidepressant. Jampala (1985) studied genetic patterns and found that a higher incidence of bulimics' relatives had histories of primary affective disorder. Bazire (1988) hypothesizes that antidepressants may benefit bulimia and major affective disorder through similar mechanisms. Siegel (1989), using an N of 1 design, found support for the hypothesized relationship between affective illness and bulimia.

Pope and Hudson (1982) performed one of the first studies on the treatment of bulimia with antidepressants, specifically imipramine. Although their sample size was small (N = 8), they discovered that 75% of those subjects who were treated with imipramine showed a significant decrease in their binging behavior. This decrease lasted from two to seven months. The

authors called for more research and noted that their study, although important, should be replicated as their study lacked a control group.

Hughes, Wells, Cunningham and Ilstrup (1986) note that bulimics who were treated with desipramine, an antidepressant, showed an 87% binge decrease rate. Their sample size decreased due to attrition, and their study used scales developed by the authors to report data. However, these scales were never checked for reliability or validity. Walsh et al. (1988) note that the monoamine oxidase inhibitor (MAOI) phenelzine used by bulimics was successful in 64% of their clients in reducing binge frequency. Pope, Hudson and Jonas (1983) believe that MAOI's are superior to other antidepressants in the treatment of bulimia. However, MAOI's have some serious side effects and require the user to be on a tyramine-free diet. This dietary restriction may be difficult to obtain with bulimics (Walsh et al., 1988).

Brotman, Herzog and Hamburg (1988) found that three out of seven of their clients who received at least one trial of antidepressants showed a significant decrease in their binging behavior. However, they note that their sample size was too small and was thus a hindrance to external validity.

Based upon the literature, using antidepressant medications in the treatment of bulimia would seem to be a logical modality, even if we are not

sure how or why these medications work or if bulimia and major affective disorder are somehow related.

It is evident that many unanswered questions remain that should be addressed in future research. One question (although not the most important one) that should be answered is what exactly causes bulimia, for if researchers are ever to find a cure for bulimia, they first have to have some idea as to what causes it. The literature points to a physiological basis and a connection between bulimia and major affective disorder. These hypotheses are supported by the relative efficacy of antidepressant agents, especially the tricyclics (See Hughes et al., 1986, etc.). However, many of these studies have flaws, such as using scales that were never checked for reliability or validity. One way to overcome this is to combine various paper-and-pencil measures with the examination of the bulimic's blood levels of the drug, similar to what Hughes et al. (1986) did. Examination of blood levels gives experimenters vital information including such data as compliance of the client in regard to using the agent as well as various levels of cholesterol, potassium, and so on. The negative side is the aversive aspect of giving blood. The present study will utilize a combination of self-reports, clinical and behavioral observations, bi-weekly weigh-ins, and chemical and urine analyses to attempt to detect the efficacy of desipramine on bulimia.

Another potential problem with chemotherapy for bulimia is that many antidepressants have side effects, some of which may be unpleasant (Baldessarini, 1985; Hyman & Arana, 1987). One way to counteract this is to use an agent that has low sedating effects and low anticholinergic effects. Hyman and Arana (1987) recommend desipramine, among other agents, in order to achieve these results. MAOI's also appear to be effective but the fact that they would require the bulimic to remain on a tyramine-free diet makes their usage unwise, especially as a front-line agent. However, their efficacy in treating bulimia should remain under investigation.

In conclusion, chemotherapy as an effective treatment modality for bulimia should remain under investigation. The present study hypothesizes that desipramine will be effective in reducing the binging and purging behaviors of bulimics, and that an adequate blood level needs to be reached before desipramine produces its desired effects. If this proves to be the case, it will only add to the support that chemotherapy is a viable treatment option for bulimia, that bulimia may somehow be linked with affective disorder, and that bulimia may have a physiological basis.

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