Serotonin Neuronal Function and Selective Serotonin Reuptake Inhibitor Treatment in Anorexia and Bulimia Nervosa

Walter Kaye, Kelly Gendall, and Michael Strober

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior and weight regulation, and disturbances in attitudes toward weight and shape and the perception of body shape. Emerging data support the possibility that substantial biologic and genetic vulnerabilities contribute to the pathogenesis of AN and BN. Multiple neuroendocrine and neurotransmitter abnormalities have been documented in AN and BN, but for the most part, these disturbances are state-related and tend to normalize after symptom remission and weight restoration; however, elevated concentrations of 5-hydroxyindoleacetic acid in the cerebrospinal fluid after recovery suggest that altered serotonin activity in AN and BN is a trait-related characteristic. Elevated serotonin activity is consistent with behaviors found after recovery from AN and BN, such as obsessionality with symmetry and exactness, harm avoidance, perfectionism, and behavioral overcontrol. In BN, serotonergic modulating antidepressant medications suppress symptoms independently of their antidepressant effects. Selective serotonin reuptake inhibitors (SSRIs) are not useful when AN subjects are malnourished and underweight; however, when given after weight restoration, fluoxetine may significantly reduce the extremely high rate of relapse normally seen in AN. Nonresponse to SSRI medication in ill AN subjects could be a consequence of an inadequate supply of nutrients, which are essential to normal serotonin synthesis and function. These data raise the possibility that a disturbance of serotonin activity may create a vulnerability for the expression of a cluster of symptoms that are common to both AN and BN and that nutritional factors may affect SSRI response in depression, obsessive–compulsive disorder, or other conditions characterized by disturbances in serotonergic pathways.


Key Words: Anorexia nervosa, bulimia nervosa, serotonin, selective serotonin reuptake inhibitors, treatment, eating disorders

Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior and weight regulation, and disturbances in attitudes toward weight and shape and the perception of body shape. In AN, there is an inexplicable fear of weight gain and unrelenting obsession with fatness even in the face of increasing cachexia. BN usually emerges after a period of dieting, which may or may not have not been associated with weight loss. Binge eating is followed by either self-induced vomiting, or by some other means of compensation for the excess of food ingested. The majority of people with BN have irregular feeding patterns, and satiety may be impaired. Although abnormally low body weight is an exclusion for the diagnosis of BN, some 25–30% of patients with BN who present to treatment centers have a prior history of AN; however, all individuals with BN have pathological concern with weight and shape. Common to individuals with AN or BN are low self-esteem, depression, and anxiety.

In certain respects, both diagnostic labels are misleading. Individuals affected with AN rarely have complete suppression of appetite, but rather exhibit a volitional, and more often than not, ego syntonic resistance to feeding drives while eventually becoming preoccupied with food and eating rituals to the point of obsession. Similarly, BN may not be associated with a primary, pathological drive to overeat; rather, like individuals with AN, those with BN have a seemingly relentless drive to restrain their food intake, an extreme fear of weight gain, and often have a distorted view of their actual body shape. Loss of control with overeating usually occurs intermittently and typically only some time after the onset of dieting behavior. Episodes of binge eating ultimately develop in a significant proportion of people with AN (Halmi et al 1991),

From the Department of Psychiatry, University of Pittsburgh, School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania (WK, KG); and Neuropsychiatric Institute and Hospital, School of Medicine, University of California at Los Angeles, Los Angeles, California (MS).

Address reprint requests to Walter H. Kaye, MD, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, 3811 O’Hara Street, Pittsburgh, PA 15213.

Received January 6, 1998; revised April 24, 1998; accepted April 30, 1998.

© 1998 Society of Biological Psychiatry

0006-3223/98/$19.00
PII S0006-3223(98)00195-4
whereas some 5% of those with BN will eventually develop AN (Hsu and Sobkiewicz 1989). Because restrained eating behavior and dysfunctional cognitions relating weight and shape to self-concept are shared by patients with either of these syndromes, and considering that transitions between syndromes occur in many, it has been argued that (Schweiger and Ficther 1997) AN and BN share at least some risk and liability factors in common.

The etiology of AN and BN is presumed to be complex and multiply influenced by developmental, social, and biological processes (Garner 1993; Treasure and Campbell 1994); however, the exact nature of these interactive processes remains incompletely understood. Certainly, cultural attitudes toward standards of physical attractiveness have relevance to the psychopathology of eating disorders; but it is unlikely that cultural influences in pathogenesis are very prominent. For one, dieting behavior and the drive toward thinness is quite commonplace in industrialized countries throughout the world, yet AN and BN affect only an estimated 0.3–0.7 %, and 1.7–2.5%, respectively, of the general female population. Moreover, the fact that numerous clear descriptions of AN date from the middle of the nineteenth century (Treasure and Campbell 1994) suggests that factors other than our current culture play an etiologic role. Second, both syndromes, AN in particular, have a relatively stereotypic clinical presentation, sex distribution, and age of onset supporting the possibility of some biologic vulnerability.

Illness Phenomenology

Variations in feeding behavior have been used to subdivide individuals with AN into two meaningful diagnostic subgroups that have been shown to differ in other psychopathological characteristics (Garner et al 1985; Strober et al 1982). In the restricting subtype of AN, subnormal body weight and an ongoing malnourished state are maintained by unremitting food avoidance; in the bulimic subtype of AN, there is comparable weight loss and malnutrition, yet the course of illness is marked by supervening episodes of binge eating, usually followed by some type of compensatory action such as self-induced vomiting or laxative abuse. Individuals with the bulimic subtype of AN are also more likely to exhibit histories of behavioral dyscontrol, substance abuse, and overt family conflict in comparison to those with the restricting subtype. Particularly common in individuals with AN are personality traits of marked perfectionism, conformity, obsessiosity, constriction of affect and emotional expressiveness, and reduced social spontaneity. These traits typically appear in advance of the onset of illness and persist even after long-term weight recovery, indicating they are not merely epiphenomena of acute malnutrition and disordered eating behavior (Casper 1990; O’Dwyer et al 1996; Srinivasagam et al 1995; Strober 1980).

Individuals with BN remain at normal body weight, although many aspire to ideal weights far below the range of normalcy for their age and height. The core features of BN include repeated episodes of binge eating followed by compensatory self-induced vomiting, laxative abuse, or pathologically extreme exercise, as well as abnormal concern with weight and shape. The DSM-IV has specified a distinction within this group between those individuals with BN who engage in self-induced vomiting or laxative, diuretic, or enema abuse (purging type), and those who exhibit other forms of compensatory action such as fasting or exercise (nonpurging type). Beyond these differences, it has been speculated (Vitousek and Manke 1994) that there are two clinically divergent subgroups of individuals with BN differing significantly in psychopathological characteristics: a so-called multi-impulsive type, in whom bulimia occurs in conjunction with more pervasive difficulties in behavioral self-regulation and affective instability, and a second type whose distinguishing features include self-effacing behaviors, dependence on external rewards, and extreme compliance. BN patients of the multi-impulsive type are far more likely to have histories of substance abuse and display other impulse control problems such as shoplifting and self-injurious behaviors. Considering these differences, it has been postulated that individuals with multi-impulsive type BN rely on binge eating and purging as a means of regulating intolerable states of tension, anger, and fragmentation; in contrast, individuals with BN who are not of this multi-impulsive type may have binge episodes precipitated through dietary restraint with compensatory behaviors maintained through reduction of guilty feelings associated with fears of weight gain.

Course of Illness

Most cases of AN emerge during the period of adolescence, although the condition can be observed in children. There is no clear consensus as of yet on whether or not prepubertal onset of the illness confers a more or less ominous prognosis (Halmi et al 1979; Theander 1985). Recovery from the illness tends to be protracted, but studies of long-term outcome reveal the illness course to be highly variable; roughly 50% of individuals will eventually have reasonably complete resolution of the illness, whereas another 30% will have lingering residual features that wax and wane in severity long into adulthood. Ten percent of people with AN will pursue a chronic, unremitting course, and the remaining 10% of those affected will
Evidence of Genetic Influences

As noted previously, there is no convincing evidence that cultural factors are the primary or most formidable determinants of these disorders; however, emerging evidence suggests that both AN and BN are familial and that clustering of the disorder in families may arise partly from genetic transmission of risk (Lilenfeld et al in press; Strober 1991). In one large family study of AN (Strober et al 1990), risk of the disorder in mothers and sisters of probands was estimated at 4%, or roughly eight times the lifetime expectancy in the general female population. Moreover, the present authors have reported recently that a more broadly defined eating disorder phenotype that differs from AN or BN in degree of severity occurs far more often in relatives of both AN and BN probands compared to relatives of normal controls. Likewise, analysis of data from a large, epidemiological sample of twins obtained via the Virginia Twin Registry (Kendler et al 1991; Walters and Kendler 1995) adds to evidence of a strong association between AN and BN. Specifically, it was found that the cotwin of a twin affected with AN was 2.6 times more likely to have a lifetime diagnosis of BN compared to cotwins of unaffected twins. In short, evidence suggests at least some sharing of familial risk and liability factors between AN and BN. This finding is of considerable importance to future family-genetic research if it should be confirmed that the broader, subclinical phenotype is more common among relatives than the narrow, more severe phenotype.

Paralleling these accounts are several reports of greater pairwise concordance rates of eating disorders in monozygotic compared to dizygotic twin pairs, with heritability estimates in the range of 50–90% for AN (Holland et al 1988; Treasure and Holland 1989) and 35–50% for BN (Kendler et al 1991); however, with the exception of reports from Kendler’s group, based on diagnostic study of the Virginia Twin Registry sample, existing accounts of differential concordance of eating disorders in twin pairs are hampered by unsystematic, and potentially biased, sampling.

As noted earlier, a range of general psychiatric symptoms are found commonly in patients with AN or BN. In many cases, they develop secondary to malnutrition and other disabling psychological effects of aberrant eating patterns; yet, in some, they clearly antedate disordered eating, or arise following recovery from low body weight or binge eating. Whether or not particular psychiatric disorders increase liability to eating disorders or are expressions of a shared underlying diathesis is a question of heuristic and clinical importance.

Several family and twin studies have examined the covariation between eating disorders and various other psychiatric conditions that co-occur with AN and BN. These studies have been reviewed in detail (Lilenfeld et al 1997; Strober 1991). With regard to major affective illness, studies of AN probands have yielded familial risk estimates in the range of 7–25%, with relative risk estimates in studies employing normal controls in the range of 2.1–3.4. Likewise, studies of BN probands have shown, with rare exceptions, that their first-degree relatives are several times more likely to develop affective disorders than relatives of control subjects. At the same time, most studies considering the effects of proband comorbidity on familial risk have shown that affective illness is more likely to be transmitted by probands with this same diagnostic comorbidity. In short, although AN and BN often co-occur with major mood disorders, unipolar depression in particular, the two conditions do not seem to express a single, shared transmitted liability.

Family studies investigating rates of substance use disorders suggest relatively low rates among relatives of restricting AN probands (Holderness et al 1994; Lilenfeld et al in press). In contrast, rates are elevated in relatives of probands with BN; however, results from two studies (Kaye et al 1996; Schuckit et al 1996) indicate that there is no evidence of a cross-transmission of BN and substance use disorder in families, whereas twin data (Kendler et al 1991) have shown that the genetic variation influencing susceptibility to alcoholism was independent of those genetic factors underlying risk for BN. Tentative evidence of independent familial transmission of obsessive-compulsive disorders and AN and BN has also been reported by the present authors (Lilenfeld et al in press). On the other hand, we have reported preliminary data suggesting a common familial transmission of AN and obsessive-compulsive personality disorder, thus suggesting the exis-
ence of a broad, genetically influenced phenotype with core features of rigid perfectionism and propensity for extreme behavioral constraint. Hence, in spite of the formidable challenges encountered in the biological study of nutritionally compromised individuals, efforts to better understand the pathophysiology of AN and BN continue to have clinical and heuristic value.

**Persistent Psychological Disturbances after Recovery from AN and BN**

People who have an eating disorder (ED) often have a variety of symptoms aside from pathological eating behaviors. Physiological symptoms include an abundance of neuroendocrine, autonomic, and metabolic disturbances. Psychological symptoms include depression, anxiety, substance abuse, and personality disorders. Determining whether such symptoms are a consequence or a potential cause of pathological feeding behavior or malnutrition is a major methodological issue in the study of EDs. It is impractical to study EDs prospectively due to the young age of onset and difficulty in premorbid identification of people who will develop an ED; however, subjects can be studied after long-term recovery from an ED. The assumed absence of confounding nutritional influences in recovered ED women raises a possibility that persistent psychobiological abnormalities might be trait-related and potentially contribute to the pathogenesis of this disorder. A limited number of studies have investigated people who have recovered from AN and BN. Although the definition of recovery from an ED has not been formalized, investigators tend to include people formerly ill with AN after they have been at a stable and healthy body weight for months or years of time and have not been malnourished or engaged in pathological eating behavior during that period of recovery. For BN, investigators tend to include subjects who have been abstinent from binging and purging for months or years of time. Some investigators include a criteria of normal menstrual cycles and a minimal duration of recovery, such as 1 year of time.

Investigators (Casper 1990; O’Dwyer et al 1996; Srinivasagam et al 1995; Strober 1980) have found that women who were long-term recovered from AN had a persistence of obsessional behaviors as well as inflexible thinking, restraint in emotional expression, and a high degree of self- and impulse control. In addition, they have social introversion, overly compliant behavior, and limited social spontaneity as well as greater risk avoidance and harm avoidance. Moreover, individuals who are long-term recovered from AN had continued core eating disorder symptoms, such as ineffectiveness, a drive for thinness, and significant psychopathology related to eating habits. Similarly, people who have recovered from BN continue to be overconcerned with body shape and weight, abnormal eating behaviors, and dysphoric mood (Collings and King 1994; Fallon et al 1991; Johnson-Sabine et al 1992; Kaye et al in press; Norring and Sohlberg 1993). Recovered AN and BN women had increased perfectionism, and their most common obsessional target symptoms were the need for symmetry and ordering/arranging. Considered together, these residual behaviors can be characterized as over concerns with body image and thinness, obsessionality with symmetry, exactness, and perfectionism, and dysphoric/negative affect. In general, pathological eating behavior and malnutrition appear to exaggerate the magnitude of these concerns. Thus, the intensity of these symptoms is less after recovery, but the content of these concerns remains unchanged. The persistence of these symptoms after recovery raises a question of whether such behaviors are premorbid traits that contribute to the pathogenesis of AN and BN.

**Studies of Neurotransmitters**

The role of biology in the etiology of AN has been proposed for the past 60 years (Russell 1970). Earlier theories raised the question of whether people with AN had a pituitary or hypothalamic disturbance. More recently, a growing understanding of neurotransmitter modulation of appetitive behaviors has raised the question of whether some disturbance of neurotransmitter function causes AN and/or BN (Fava et al 1989; Leibowitz 1986; Morley and Blundell 1988). It is possible that disturbances of brain neuropeptides and/or monoamines could contribute to other symptoms and behaviors, such as neuroendocrine or autonomic abnormalities, or alterations of mood and behavior, in people with AN or BN. It is important to emphasize that monoamine or neuropeptide disturbances could be a consequence of dietary abnormalities, or premorbid traits that contribute to a vulnerability to develop AN or BN. One way to tease apart cause and effect is to study people with AN or BN at various stages in their illness; that is, while symptomatic and after recovery.

**Neuropeptides**

Multiple neuroendocrine abnormalities have been documented in AN and BN (Sharp and Freeman 1997), including alteration of the hypothalamic–pituitary–gonadal axis, the hypothalamic–pituitary–adrenal axis, thyroid system, growth hormone secretion, and fluid conservation as well as autonomic instability and reduced metabolic function. For the most part, these neuroendocrine disturbances are state-related and tend to normalize after clinical recovery.
Starvation-induced alterations of neuropeptide activity probably contribute to neuroendocrine dysfunctions in the eating disorders. For example, corticotropin-releasing hormone (CRH) alterations contribute to hypercortisolemia (Gold et al 1986; Kaye et al 1987) and neuropeptide Y (NPY) alterations may contribute to amenorrhea (Kaye et al 1990). Hypersecretion of vasopressin and reduced cerebrospinal fluid (CSF) oxytocin in underweight AN subjects may maintain or exacerbate the persistent preoccupation with the adverse consequences of food intake (Demitrack et al 1990). Hence, alterations in a number of different peptides could contribute to and perpetuate the characteristic psychophysiological disturbances, such as reduced feeding, in acutely ill AN and BN patients. Many people with AN or BN cannot easily “reverse” their illness. In AN, malnutrition may contribute to entering a downward spiraling cycle with malnutrition sustaining and perpetuating the desire for more weight loss and dieting. Symptoms, such as increased satiety, as well as obsessions and dysphoric mood, may be exaggerated by these neuropeptide alterations and thus contribute to this downward spiral. Even after improved nutrition and weight gain, many people with AN have much difficulty normalizing their behavior. For example, abnormal eating attitudes, affective disturbances, and menstrual dysfunction may persist despite weight restoration (Copeland et al 1995; Falk and Halmi 1982). While neuroendocrine and neuropeptide disturbances do not appear to be a permanent feature or cause of AN, these disturbances are strongly entrenched and are not easily corrected by improved nutrition or short-term weight normalization. The fact that neuroendocrine and neuropeptide disturbances are not found after long-term recovery suggests that therapy must be sustained for months after weight normalization.

Serotonin Neuronal Activity

There has been considerable interest in the role that serotonin (5-HT) may play in AN and BN (Blundell 1992; Brewerton 1995; Jimerson et al 1990; Kaye and Weltzin 1991; Treasure and Campbell 1994). A substantial number of studies have shown alterations in 5-HT activity in the ill state. Although less well studied, 5-HT disturbances appear to persist after recovery. In addition, people with AN and BN (see below) respond to antidepressants in placebo-controlled trials.

5-HT pathways play an important role in postprandial satiety. Treatments that increase intrasynaptic 5-HT, or directly activate 5-HT receptors, tend to reduce food consumption, whereas interventions that dampen serotonergic neurotransmission or block receptor activation reportedly increase food consumption and promote weight gain (Blundell 1984; Leibowitz 1986). Moreover, central nervous system (CNS) 5-HT pathways have been implicated in the modulation of mood, impulse regulation and behavioral constraint, and obsessionality. They also affect a variety of neuroendocrine systems.

When underweight, patients with AN have a significant reduction in basal concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the CSF compared to healthy controls (Figure 1) (Demitrack et al 1995; Kaye et al 1988b), as well as blunted plasma prolactin response to 5-HT activity (Hadigan et al 1995) and reduced 3H-imipramine binding (Weizman et al 1986). Together, these findings suggest reduced serotonergic activity, which could be secondary to a diet-induced reduction of availability of the amino acid, tryptophan, the precursor of 5-HT. In contrast, CSF concentrations of 5-HIAA are reported to be elevated (Kaye et al 1991a) and neuroendocrine responses to 5-HT-stimulating drugs are normalized (O’Dwyer et al 1996) in women who are long-term weight recovered from AN. These contrasting findings of reduced and heightened serotonergic activity in acutely ill and long-term recovered AN individuals, respectively, may seem counterintuitive; however, since dieting lowers plasma tryptophan levels in otherwise healthy women (Anderson et al 1990), resumption of normal eating in AN may unmask intrinsic abnormalities in serotonergic systems that mediate certain core behavioral or temperamental underpinnings of risk and vulnerability.

Considerable evidence also exists of dysregulation of serotonergic processes in people who are ill with BN. This includes blunted prolactin response to the 5-HT receptor agonists m-chlorophenylpiperazine (m-CPP) (Brewerton et al 1992; Levitan et al 1997), 5-hydroxytryptophan (Goldbloom et al 1990a), and dl-fenfluramine (Jimerson et al 1997; McBride et al 1991), increased platelet 5-HT uptake (Goldbloom et al 1990b), reduced platelet imipra-
mine binding capacity (Marazziti et al. 1988), and enhanced migraine-like headache response to m-CPP challenge (Brewerton et al. 1988). Moreover, acute perturbation of serotonergic tone by dietary depletion of tryptophan has also been linked to increased food intake and mood irritability in women with BN compared to healthy controls (Weltzin et al. 1994). Whereas ill BN have normal CSF 5-HIAA levels (Figure 1), women who are long-term recovered from BN have elevated concentrations of 5-HIAA in the CSF (Kaye et al. in press).

Together, these data show that both recovered AN and BN women have elevated CSF 5-HIAA concentrations. It has been found that low levels of CSF 5-HIAA are associated with impulsive and nonpremeditated aggressive behaviors, which cut across traditional diagnostic boundaries. Behaviors found after recovery from AN and BN, such as obsessions with symmetry, exactness, and perfectionism, and negative affect, tend to be opposite in character to behaviors displayed by people with low 5-HIAA levels. Together, these studies contribute to a growing literature that suggests that CSF 5-HIAA concentrations may correlate with a spectrum of behavior. These data support the hypothesis (Cloninger et al. 1993) that increased CSF 5-HIAA concentrations may be associated with exaggerated anticipatory overconcern with negative consequences, while the lack of such concerns may explain impulsive, aggressive acts that are associated with low CSF 5-HIAA.

These data raise the possibility that a disturbance of 5-HT activity may create a vulnerability for the expression of a cluster of symptoms that are common to both AN and BN. The possibility of a common vulnerability for AN and BN may seem puzzling given well-recognized differences in behavior in these disorders; however, recent studies suggest that AN and BN have a shared etiologic vulnerability (Kendler et al. 1991). Other factors, that are independent of a vulnerability for the development an eating disorder, may contribute to the development of eating disorder subgroups. For example, people with restricting-type AN have extraordinary self-restraint and self-control. The risk for obsessive–compulsive personality disorder is elevated only in this subgroup and in their families and shows a shared transmission with restricting-type AN (Lilenfeld et al. in press). In other words, an additional vulnerability for behavioral over-control and rigid and inflexible mood states, combined with a vulnerability for an eating disorder, may result in restricting-type AN.

The contribution of 5-HT to specific human behaviors remains uncertain. That is, 5-HT has been postulated to contribute to temperament or personality traits, such as harm avoidance (Cloninger 1987) or behavioral inhibition (Soubrie 1986), or to categorical dimensions such as obsessive–compulsive disorder (OCD) (Barr et al. 1992), anxiety and fear (Charney et al. 1990), or depression (Graheme-Smith 1992) as well as satiety for food consumption. Importantly, these symptoms persist in AN and BN after recovery.

BN, the most common ED, may be the prototypic expression of a disturbance of 5-HT activity that contributes to the pathogenesis of eating disorders. Clinically, people with BN have extremes of eating and behavior. They tend to eat few normal meals. They tend to either diet or overeat. Similarly, they tend to fluctuate between minimization and inhibition of mood states and extremes of mood and catastrophic over-concerns. These clinical observations, coupled with data from studies in ill and recovered BN women, lead to the speculation that the 5-HT system in people with BN is inherently unstable and poorly modulated (Figure 2). Certain traits, such as restricted eating and obsessive perfectionism, and exactness, harm avoidance, and negative affect might be consistent with increased 5-HT transmission in a nondieting state. In contrast, a diet-induced reduction in synaptic 5-HT release could result in a reduction of this dysphoric state, but
might lead in turn to extremes of unstable mood and binge eating. It is possible that women with such an inherent modulatory defect in 5-HT function may be prone to develop an ED. Because of their modulatory 5-HT defect, they cannot respond appropriately and precisely to stress or stimuli, or modulate their affective states. They may learn that extremes of dietary intake, by effects on plasma tryptophan, are a means by which they can crudely modulate their brain 5-HT functional activity. Several investigators (Jimerson et al 1992; Kaye et al 1988a) have proposed a model in which individuals with BN may restrict eating or overeat as a means of self-modulating 5-HT activity. That is, eating or binge episodes could alter the tryptophan to large neutral amino acid ratio in plasma, which in turn alters tryptophan availability to the brain, which results in changes in 5-HT synthesis and release (Fernstrom and Faller 1978). In fact, recent studies (Weltzin et al 1994) show ill patients with BN, after tryptophan depletion, have an increase in labile and dysphoric mood and overeat compared to control women, supporting the possibility that women with BN have a fragile and dysregulated 5-HT system that is vulnerable to dietary manipulations.

### Treatment of Bulimia Nervosa

It is fair to say that progress to date in establishing the efficacy of specific psychological and pharmacologic therapies for EDs has been more dramatic for BN than for AN (Arnow 1997). With regard to psychotherapy, although the number of controlled clinical trials are still few in number, most indicate that cognitive behavior therapy (CBT) is an effective treatment for upwards of 60–70% of individuals with BN, with remission of binge eating and purging achieved in some 30–50% of cases (Connors et al 1984; Fairburn et al 1993; Kirkley et al 1985; Wolf and Crowther 1992). Evidence for the efficacy of antidepressant pharmacotherapy in BN is impressive; however, the benefits may diminish over time in a significant proportion of individuals with BN who respond initially, and only a minority have complete suppression of their symptoms with antidepressant monotherapy (Agras et al 1992; Crow and Mitchell 1996; Fluoxetine Bulimia Nervosa Collaborative Study Group 1992; Hoffman and Halmi 1993; Jimerson et al 1996; Kaye et al in submission; Mitchell and de Zwaan 1993; Mitchell et al 1990, 1993; Russell 1988; Walsh 1991a).

The results of most double-blind, placebo-controlled randomized trials reported to date indicate that antidepressants show at least some superiority over placebo in reducing the frequency of binge eating episodes (Walsh 1991b). In addition, some studies show a reduction in intensity of some other symptoms commonly seen in BN, such as preoccupation with food and depression (Goldbloom and Olmsted 1993). These findings have been demonstrated with a variety of antidepressive medications, including tricyclic antidepressants (TCAs) (imipramine, desipramine, clomipramine, amitriptyline) (Agras et al 1987; Barlow et al 1988), monoamine oxidase inhibitors (MAOIs) (phenelzine, isocarboxazid) (Walsh et al 1984), and selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, fluvoxamine) (Goldstein et al 1995). Patients participating in these trials typically reported from 8 to 10 episodes of binge eating per week at baseline. The “average” decrease in binge frequency for patients receiving the antidepressant medication was about 55%, with wide variation across studies. Placebo responses were similarly variable, but were generally less than half the size of the response for the active treatment; however, only a minority of the patients actually achieved full abstinence from binging and purging behaviors (Mitchell et al 1997). Most trials have shown no correlation between improvement in mood and reduction in BN symptoms. In addition, antidepressants suppress bulimic symptoms also in non-depressed bulimic patients, suggesting a mode of action other than through their antidepressant effects (Blouin et al 1989). In some studies, the patients receiving the antidepressive medication demonstrated a significant increase in dietary restraint and a reduction in the tendency for stressors to trigger binge eating.

There is little evidence for superiority of response to a single class of medication. Thus, differences in side effects may be a significant factor in the clinical choice of the antidepressant. The dosage level needed to achieve an effect appears to be similar to that required in major depression, with a tendency for higher dosages (e.g., 200–300 mg/day of the relevant TCA) to be more effective (Walsh 1991b). The time course of action of the medications also appears to be similar to that found in depression, with improvement occurring over the course of several weeks. Improvement in frequency of self-induced vomiting generally parallels the decrease in binging. Treatment failure should be considered only if adequate doses have been administered for 8–12 weeks. Fluoxetine 60 mg/day has proved significantly superior to 20 mg/day and to placebo in the reduction of binge eating and BN-related features (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992). This dosage has been shown to be safe with minimal adverse effects even over an extended treatment period. Other antidepressants have not been studied systematically in the treatment of BN. Bupropion is contraindicated in BN patients, as it has been associated with increased risk of seizures (Horne et al 1988).

The question of how long to continue antidepressant therapy in BN has not been addressed systematically, as
most trials have incorporated only a relatively brief duration of treatment. A few follow-up studies extending from 4 to 24 months have found a high relapse rate upon the discontinuation of the antidepressant medication (Agras 1997). As BN itself often runs a chronic course with significant rate of relapse, antidepressants apparently have to be continued for prolonged periods of time in patients responding well in the initial stages of treatment. It should be noted, however, that attenuation of the antibinge effect of the antidepressant has been noted over time.

Five studies (Agras et al 1992; Fichter et al 1991; Leitenberg et al 1994; Mitchell et al 1990; Walsh et al 1997) have been published or presented to date that assessed the relative efficacy of combining psychotherapy (in most trials of the CBT type) and antidepressants for the management of BN, compared with the isolated treatments themselves. Although differing in many respects, these studies suggest that the improvement in bulimic symptoms with CBT alone was greater than with the medication alone. Adding medication to the psychotherapy generally did not improve significantly the outcome over psychotherapy alone in terms of eating behaviors, nor did it increase the speed of the therapeutic response; however, one prolonged follow-up evaluation found that combined treatment was more effective on a number of eating variables than CBT alone (Agras et al 1992). Another study showed the superiority of combined therapy in reducing the rates of anxiety and depression (Mitchell et al 1990).

Treatment of Anorexia Nervosa

People with AN have responded less effectively to treatment (Herzog et al 1992). Extended hospitalizations can be lifesaving because such treatment can restore weight to emaciated people, which, in turn, reverses medical complications; however, hospitalizations can be lengthy and expensive. In fact, the hospital utilization rate for people with AN is higher than for any other psychiatric disorder, aside from schizophrenia and organic disorders (McKenzie and Joyce 1992). Moreover, relapse after hospitalization has been high (Russell et al 1987).

The evaluation of the efficacy of medications in augmenting weight gain in AN is limited, because most trials have been conducted in outpatients or inpatients participating in behavioral and nutritional ED programs, which are themselves efficient in the short run. Nevertheless, in these settings controlled trials have not provided consistent evidence for the efficacy of antidepressant medications in the treatment of AN (Biederman et al 1985; Gross et al 1981; Lacey and Crisp 1980). Cyproheptadine hydrochloride, a 5-HT antagonist, may increase the rate of weight gain in restricting-type AN patients (Halmi et al 1986) but only in high doses (Goldberg et al 1979; Vigersky and Loriaux 1977). Limited efficacy of pharmacologic and psychological treatment in AN may be due, in part, to the fact that past treatments have mainly focused on attempts to increase the rate of weight gain of emaciated patients in a hospital setting. Inpatient treatment, consisting of nursing care, behavior modification, and supportive psychotherapy, succeeds in restoring the weight of most emaciated AN patients. Thus, it is difficult to prove that an active medication is effective in such a setting.

Some, but not all (Strober et al 1997b), recent studies that have focused on preventing relapse show more promise. Several psychotherapies specifically developed to treat AN appear to show reduced relapse at a 1–2-year follow-up (Russell et al 1987; Treasure et al 1996). Our group (Kaye et al 1991b; in submission) has found in separate open and double-blind placebo-controlled studies that fluoxetine improved outcome and reduced relapse after weight restoration. That is, fluoxetine was associated with a significant reduction in core ED symptoms, depression, anxiety, and obsessions and compulsions. In a recent double-blind, placebo-controlled study, our group found that fluoxetine, when given after weight restoration, significantly reduces the extremely high rate of relapse normally seen in AN. Subjects were started on fluoxetine \((n = 16)\) or placebo \((n = 19)\) after inpatient weight restoration, discharged from the hospital, and followed for 1 year as outpatients. Ten of 16 (63%) subjects on fluoxetine remained well over 1 year of outpatient follow-up, whereas only 3 of 19 (16%) remained well on placebo \((p = .006)\). Figure 3. Fluoxetine administration was associated with a significant weight gain and a significant reduction in obsessions and compulsions. Thus fluoxetine improves outcome in AN by reducing symptoms and helps maintain a healthy body weight in outpatient treatment.

Our group (Ferguson et al in press) and others (Atti et al 1998) have found that SSRIs are not useful when people with AN are malnourished and underweight. As noted by Tollefson (1995), SSRIs are dependent on neuronal release of 5-HT for their action. If the release of 5-HT from presynaptic neuronal storage sites was substantially compromised, and net synaptic 5-HT concentration was negligible, a clinically meaningful response to an SSRI might not occur. In fact, malnourished individuals with AN have reduced CSF 5-HIAA, the major 5-HT metabolite in the brain (Kaye et al 1984), suggesting reduced synaptic 5-HT. This could be due to reduced availability of tryptophan, the essential amino acid precursor to 5-HT (Schweiger et al 1986).

This link between dietary intake and SSRI efficacy is supported by data that have repeatedly shown that dieting in healthy normal-weight and obese women reduces try-
Serotonin and SSRIs in Eating Disorders

Figure 3. Survival curve showing proportion of anorexia nervosa patients remaining well on fluoxetine or placebo after weight restoration.

Tophan availability and thereby limits potential serotonergic production (Anderson et al 1990; Gatti et al 1993; Goodall 1990; Walsh et al 1995; Wolfe et al 1997). Moreover, studies in animals show that food restriction decreases 5-HT and its synthesis rate in the brain (Haleem and Haider 1996) and down-regulates the density of 5-HT transporters (Huether et al 1997). Finally, depletion of tryptophan, the precursor of 5-HT, reverses the effects of SSRIs in depressed patients (Barr et al 1994; Bremner et al 1997; Delgado et al 1990). In addition, in the patients studied by Delgado et al (1990), plasma tryptophan was inversely related to depression scores. In AN, weight restoration normalizes nutrition, and CSF 5-HIAA concentrations become elevated (Kaye et al 1991a). These changes in nutrients and 5-HT activity may account for why individuals with AN may become responsive to fluoxetine after weight restoration.

Other Potential Effects of Nutrition on Serotonin Activity and SSRI Efficacy

Impaired 5-HT functional activity could also be a consequence of nutrients other than tryptophan, which are essential to normal 5-HT synthesis and function, and are reduced in underweight AN patients (McClain et al 1993; Mira et al 1989; Nunez et al 1995; Rock and Curran-Celentano 1994; Rock and Vasantharajan 1995). These include insulin activity, essential fatty acids, zinc, and pyridoxine (vitamin B6). Insulin mediates the increased brain uptake of tryptophan and 5-HT synthesis following carbohydrate ingestion, and the low basal and post-ingestive insulin concentrations observed in underweight AN patients (Alderdice et al 1985) may hamper this process. Very low-fat diets, as typically consumed by women with AN, have been found to diminish neuronal 5-HT activity in animal studies (Muldoon et al 1992). In addition, the type of dietary fat consumed determines the biophysical properties of cell membranes and hence influences neurotransmitter receptor function. Specifically, it has been hypothesized that an inadequate n-3 fatty acid intake adversely affects serotonergic function (Hibbeln and Salem 1995).

Zinc also influences membrane stability to the extent that zinc deficiency increases membrane fluidity, causing the loss of receptor function (McClain et al 1993). Poor zinc status has been observed in individuals with AN (Rock and Curran-Celentano 1994), which may contribute to the ineffectiveness of SSRIs during the acute stage of the illness. The B vitamins are also involved in metabolic pathways influencing 5-HT availability. Vitamin B12 and folate are required for the formation of tetrahydrobiopterin, which is a hydroxylase cofactor in the rate-limiting step of 5-HT synthesis (Coppen et al 1989). Vitamin B6, in the form of pyridoxal-5-phosphate, is a cofactor required in the reaction that converts 5-hydroxytryptophan to 5-HT (Dakshinamurti et al 1990; Sharma and Dakshinamurti 1994). Dietary deficiency and lowered biochemical activity of these B vitamins in some patients with AN (Mira et al 1989; Nunez et al 1995; Rock and Curran-Celentano 1994; Rock and Vasantharajan 1995) may therefore compromise the ability of SSRIs to facilitate serotonergic function.

An alternative possibility is that reduced serotonergic activity in dieting women and women underweight with AN is mediated through low levels of gonadal steroids that are observed in malnourished states (Pirke et al 1989; Wakeling et al 1979). Estrogen has been found to stimulate significant increases in the density of central 5-HT2A binding sites (Fink et al 1996) and 5-HT transporter binding sites (McQueen et al 1996), to inhibit monoamine oxidase activity (Chakravorty and Halbreich 1997), and to be positively correlated to platelet 5-HT content (Guicheney et al 1988). A deficiency of estrogen in malnutrition may, therefore, thwart the functional activity of the serotonergic system and the potential responsiveness to SSRI medication.

In summary, AN is a condition in which inadequate nutrition appears to impair SSRI efficacy. It has also been shown that people with BN show signs of starvation when bingeing and purging (Pirke et al 1985, 1989). Although not as well studied, it is possible that malnutrition could also compromise SSRI efficacy in individuals with BN. These data raise the possibility that nutritional factors may affect SSRI response in depression, OCD, or other conditions characterized by disturbances in serotonergic path-
ways. When patients do not respond to one SSRI medication, physicians often switch to another SSRI medication. Another strategy would be to assess nutritional status. Better nutrition might serve to improve SSRI efficacy. The possibility that suboptimal nutritional status is responsible for nonresponse to SSRI treatment in depression or OCD remains to be determined.

Summary

Emerging data support the possibility that substantial biologic vulnerabilities contribute to the pathogenesis of AN and BN. The development of an ED is often attributed to the effects of our cultural environment, such as mass media, on body image; however, although all women in our society are exposed to cultural mores that value slimness, only a small percentage of women exposed to these messages develop an ED. Thus, it is possible that there may be an underlying biologic diathesis that places someone “at risk” for developing BN. Similar shifts in the understanding of the pathophysiology of obesity have been driven by the discovery of potentially new mechanisms of weight regulation.

This work was presented at the Neuroscience Discussion Forum “A Decade of Serotonin Research” held at Amelia Island, Florida in November 1997. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Eli Lilly and Company.

References

Coppen A, Swade C, S.A. J, Armstrong RA, Blair JA, Leeming
Serotonin and SSRIs in Eating Disorders

BIOL PSYCHIATRY
1998;44:825–838


Hoffman L, Halmi KA (1993): Psychopharmacology in the


Serotonin and SSRIs in Eating Disorders


