

New Directions in Treatment Research of Anorexia and Bulimia Nervosa

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Although considerable progress has been made in the understanding and treatment of anorexia and bulimia nervosa, a substantial proportion of people with these disorders have a limited response to treatment. Treatment strategies used in eating disorders have tended to be adopted from therapies that were devised to treat other psychiatric illnesses. Recent studies suggest that eating disorders are independently transmitted familial liabilities with a unique pathophysiology. These new findings raise the possibility that an improved understanding of the pathogenesis of eating disorders will generate more specific and effective psychotherapies and pharmacologic interventions. Biol Psychiatry 1999;45:1285-1292
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Key Words: Anorexia, bulimia nervosa, pharmacotherapy, psychotherapy

Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are complex, multiply determined disorders of unknown etiology that occur preponderantly in young women (American Psychiatric Association 1994). An unusual, morbid preoccupation with weight and shape bridges the two syndromes, yet distinctive patterns of weight regulation and feeding behavior supports the validity of their clinical differentiation. In AN, a seemingly purposeful, ego syntonic restriction of food intake culminating in profound emaciation is pathognomonic. Two AN patient subgroups have been identified by consummatory behavior: a restricting type, in whom a relatively enduring pattern of dietary restriction is characteristic, and a binge eating type, in whom episodes of binge eating or purging coincide with dietary restriction and subnormal body weight. In BN, average body weight is maintained although the illness may, nevertheless, be precipitated by

dieting and weight loss, and further weight loss may be desired. Individuals with BN suffer recurring disinhibition of restraint resulting in cycles of binge eating and compensatory actions including self induced vomiting, abuse of laxatives/diuretics, and pathologically extreme exercise and restricting (Kaye and Strober, in press).

The past decade bears witness to substantial advances in our knowledge of the pathogenesis of eating disorders and the efficacy of certain types of structured psychotherapies and antidepressant pharmacotherapies in their treatment (Table 1). In the area of treatment research, AN stands in sharp contrast to BN in the dearth of large-scale, randomized controlled clinical trials of therapeutic modalities (Agras 1991; Mitchell et al 1993; Wilson and Fairburn 1993). In this article, we highlight these studies as a point of departure for considering potentially promising new avenues of treatment research.

It is to be noted that recent treatment studies in eating disorders tend, by and large, to be based on intervention paradigms and strategies previously tested on psychiatric disorders that co-occur frequently with AN and BN, such as depression, anxiety, and substance use. Although some risk factors in eating disorders may be shared with mood and anxiety disorders (e.g., Fairburn et al 1997), a number of recent family and twin studies (see Lilenfeld et al 1997) suggest that eating disorders and the conditions that are comorbid with them tend to sort independently in families or have unique genetic liability factors. Thus, the search for unique treatment modalities, targeting underlying vulnerabilities that contribute specifically to the pathogenesis of eating disorders, remains a theoretically and clinically justifiable endeavor.

Anorexia Nervosa (AN)

AN was first described more than a century ago, although its notation in archival medical literature is far older (Habermas 1989). Its early treatment derived largely from psychoanalytic, family systems, or behavioral paradigms, until the pioneering work of Bruch (1973) broadened our understanding of its psychological underpinnings in impaired self-concept, body image, and interoceptive processes. Still, the first generation of controlled treatment studies were narrowly focused on testing the value of behavior modification in increasing the rate of weight gain in hospitalized, emaciated patients, or the efficacy of

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Received September 11, 1998; revised February 15, 1999; accepted February 19, 1999.

Table 1. Landmark Studies in Eating Disorders

Author and Year	Event
Hobbes 1908	First description of a possible case of anorexia nervosa in 1668 in England.
Gull 1874	First case series of restricting anorexia nervosa published.
Wulf 1932	First description of what is thought to be bulimia nervosa.
Stunkard et al 1955	First description of a night time binge eating syndrome.
Stunkard 1959	First formal description of what is thought to be binge eating disorder.
Bruch 1973	Bruch described impaired self-concept, body image, and interoceptive processes in anorexia nervosa.
Russell 1979; Garner and Garfinkel 1979	First acknowledged description of bulimia nervosa in the literature. Eating Attitudes Test developed to measure the intensity of symptoms in anorexia nervosa.
Casper et al 1980; Garfinkel et al 1980	Recognition of distinct purging and restriction subtypes of anorexia nervosa.
Fairburn 1981	First cognitive behavior therapy study for the treatment of bulimia nervosa.
Gross et al 1981	The first of a range of psychopharmacotherapy trials in anorexia nervosa showing unimpressive results.
Pope and Hudson 1982; Walsh et al 1982	Report that tricyclic antidepressants decrease binge eating in bulimia nervosa.
Rosen and Leitenberg 1982	Monoamine oxidase inhibitors found to decrease binge eating in bulimia nervosa. Exposure and response prevention therapy described for bulimia nervosa.
Garner et al 1983	Eating Disorder Inventory developed to measure eating disorder severity, subtypes and treatment outcome.
Russell et al 1987	Family therapy found to be superior to individual supportive therapy in young, nonchronic anorexia nervosa patients.
Henderson and Freeman 1987	The Bulimic Investigatory Test, Edinburgh developed to measure symptoms and severity of bulimia nervosa.
Cooper et al 1989	Eating Disorder Examination, a structured interview for eating disorder diagnosis developed.
Agras et al 1992; Mitchell et al 1990	First investigations of the comparative efficacy of psychotherapy and pharmacotherapy in bulimia nervosa: Psychotherapy and cognitive behavior therapy superior to pharmacotherapy alone.
Gwirtsman et al 1990; Kaye et al 1991b	Uncontrolled trials suggest fluoxetine is helpful during weight maintenance phase of anorexia nervosa.
Kendler et al 1991	Modest evidence for genetic influences in bulimia nervosa reported.
Spitzer et al 1991	Binge eating disorder defined as a distinct disorder.
Fairburn et al 1993	Interpersonal psychotherapy shown to be equivalent to cognitive behavior therapy in treatment of bulimia nervosa.
Collier et al 1997; Enoch et al 1998; Sorbi et al 1998	Evidence for an association of a polymorphism for the $2A$ serotonin receptor in anorexia nervosa.

adjunctive pharmacologic treatment with either neuroleptic or antidepressant drugs. This work showed that weight gain could be achieved in many patients through a combination of supportive nursing care and behavioral techniques, whereas pharmacotherapy proved to have little incremental advantage in the treatment of severely ill patients (Jimerson et al 1996).

A more recent series of randomized controlled studies has examined the efficacy of various types of psychological therapies in promoting weight gain in acutely ill patients (Channon et al 1989; Crisp et al 1991; Treasure et al 1995), or in preventing relapse after restoration of normal body weight (Russell et al 1987). Overall, the results indicate that substantial improvement in body mass and general psychosocial adjustment can be achieved in some anorectic subjects using cognitive behavioral, psychoeducational, and family therapy techniques (in some studies coupled with dietary counseling), although treatment gains are not as robust in patients with more chronic, longstanding disability. In addition, several studies have showed that fluoxetine reduced relapse and obsessionality when administered after weight restoration in women with anorexia nervosa (Kaye et al 1991b; Kaye et al 1997). Unambiguous interpretation of these data is, however, hampered by a variety of methodological shortcomings across the studies, including small sample sizes, significant drop-out rates, initial use of inpatient treatment for medically compromised patients, and importantly, absence of longer-term follow-up assessment of the durability of these gains in preventing relapse. In summary, improvements in the treatment of AN remains an issue of immense clinical and public health importance considering that AN is a chronic, relapsing illness (Herzog et al 1992) with substantial and costly medical morbidity (McKenzie and Joyce 1992) for a sizable minority of patients. Hence, it is encouraging that the efficacy of psychological therapies and serotonergic antidepressants in reducing risk of relapse in weight restored patients with AN is now being tested by several investigative groups.

Bulimia Nervosa (BN)

BN has been the focus of clinical study for only two decades, yet a considerable number of controlled clinical trials have demonstrated the efficacy of both antidepressant medications (Walsh 1991a; Mitchell et al 1993) and psychological therapies (cognitive behavior therapy (CBT) in particular) (Fairburn et al 1993) in reducing the frequency of binge eating and purging. In addition, there are improvements with these psychological interventions in certain core features of the illness such as body dissatisfaction, pursuit of thinness, and perfectionism (Fairburn et al 1993; Garner et al 1993). Even so, these

findings are counterbalanced by the more sobering reality that medication alone produces full remission in only a minority of patients, many patients require multiple trials of medication before they achieve clinically significant improvement, drop-out rates in controlled clinical trials due to adverse events are not inconsequential, and relapse during continuation therapy is high.

With regard to psychological treatment, the evidence seems to suggest that CBT alone produces higher rates of full remission than does antidepressant monotherapy (Agras et al 1992; Walsh et al 1997). Even so, some 40%–60% of patients who have participated in studies of CBT remain symptomatic to some degree upon completion of acute treatment (Agras et al 1992; Garner et al 1993; Wilson and Fairburn 1993). Psychological therapies may vary in overall spectrum of efficacy. For example, direct comparisons of CBT with other psychological treatments suggest this modality is more effective than psychodynamically oriented supportive expressive psychotherapy in reducing core symptoms of BN (Garner et al 1993; Walsh et al 1997), and is more effective than a strictly behavioral treatment in preventing early relapse into dietary restriction, binge eating, and purging (Fairburn et al 1993). The mechanisms through which these treatments actually achieve their effects are not well understood, but are assumed to be more complex than originally thought. Thus, Fairburn et al (1993), in a study comparing the effects of CBT, interpersonal therapy (IPT), and pure behavior therapy, showed that IPT, that studiously avoided any direct reference to abnormal eating attitudes or dietary behaviors, achieved long-term benefits in controlling binge eating and purging equal to those obtained with CBT.

How long to continue treatment once binge eating abates to maximally protect against risk of relapse or recurrence is a question that remains unanswered. Indeed, with respect to antidepressant therapy, relapse risk during continuation therapy in BN (Walsh et al 1991b) may be higher than that typically observed in studies of continuation therapy in unipolar depression (Keller and Boland 1998). Moreover, factors that differentially predict longer-term outcome within and across treatment modalities remain largely unstudied (Jimerson et al 1996), just as the question of whether or not combination therapy with CBT and antidepressant drugs truly has additive or synergistic effects remains unsettled. Two recent studies (Agras et al 1992; Walsh et al 1997) have suggested that combined treatment may have an advantage over CBT alone in reducing binge eating and purging, but the incremental benefit was modest at best. In this same regard, Agras et al (1992) showed that CBT combined with desipramine administered for 24 weeks was more effective than both CBT

alone and CBT plus 16 weeks of desipramine in reducing dietary preoccupation and emotional eating.

In summary, a truly optimal therapeutic strategy for BN has yet to be identified within a range of possible treatment algorithms. Critically important questions remain unstudied, including the optimal duration of either psychosocial or antidepressant therapies needed to sustain effects achieved during acute phase treatment, mechanisms underpinning possible synergistic effects of combined treatment, predictors of differential treatment outcomes, reasons for a more rapid decay of acute antidepressant treatment effects in BN compared to depression, and the anticipated effects of crossing over to alternative modalities of treatment when initial treatment fails.

Pathophysiology

It is hard to dismiss outright the relevance of cultural pressures toward thinness in the pathogenesis of eating disorders (Strober 1995), but even if the disorders are influenced pathoplastically by culturally reinforced attitudes regarding ideal shape and weight, these are not likely to be preeminent causal determinants. As common as dieting behavior and the pursuit of thinness is in industrialized countries throughout the world, AN and BN affect only an estimated 0.3%–0.7% and 1.5%–2.5%, respectively, of females in the general population (Hoek 1995). This disparity, combined with clear evidence of the syndromes' existence dating back several centuries, their stereotypic presentation, predominance in females, and developmentally specific age-of-onset distribution underscore the role played by more complex interactive biological and environmental risk and vulnerability factors (Kaye and Strober in press).

Adding further impetus to this renaissance of interest in complex biopsychosocial models of etiopathogenesis is mounting evidence that both AN and BN are familial and heritable disorders (see Lilenfeld et al 1997; Strober 1995; Kendler et al 1991; Bulik et al 1998). Moreover, there is evidence of transmission of a more broadly defined subthreshold phenotype of extreme weight and shape related anxiety (Lilenfeld et al 1998), as well as personality traits common to individuals with eating disorders, including behavioral constraint, perfectionism, and rigidity (Lilenfeld et al 1997). Recent studies have shown that after recovery from AN and BN there is a persistence of overconcern with body image and thinness, elevated harm avoidance, dysphoric/negative affect, and obsessional symmetry, exactness, and perfectionism (Casper 1990; Kaye et al 1998, Srinivasagam et al 1995). Recent observations have also shown an elevation of CSF 5-HIAA, the major metabolite of serotonin in the brain, after long-term

clinical recovery from AN and BN (Kaye et al 1991a; Kaye et al 1998). Importantly, behaviors in people recovered from AN and BN tend to be opposite in character to the impulsive and aggressive behaviors displayed by people with low 5-HIAA levels (Stein et al 1993). Together, these data support the hypothesis that increased CSF 5-HIAA concentrations may be associated with exaggerated anticipatory overconcern with negative consequences (Cloninger 1987), although the lack of such concerns may explain impulsive, aggressive acts that are associated with low CSF 5-HIAA. Moreover, increased CSF 5-HIAA might reflect an overactive serotonin system that could contribute to behavioral constraint, obsessiveness, and inhibition of appetite (Soubrie 1986; Spont 1992). Increased serotonin activity could make people specifically vulnerable to developing an eating disorder as well as certain core phenotypic aspects of these disorders, including anxious dysphoria, obsessional thinking, perseveration, and cognitive distortions of the aversive consequences of eating and weight gain (Kaye and Strober in press). These processes could be further enhanced by malnutrition triggered changes in hypothalamic neuropeptides that modulate aversively conditioned learning (Demitrack et al 1990). Extreme dieting, by its effects on plasma tryptophan, the precursor of serotonin, could be a means of reducing brain serotonin functional activity (Kaye et al 1988) and thus briefly reverse dysphoric affects (Steinberg et al 1990).

Implications for Future Treatment Research

Molecular Pharmacology

Antidepressants do not have actions specific to eating disorders. Moreover, the early hypothesis that antidepressants would have a particular value in the treatment of BN because the disorder had causative mechanisms shared in common with primary mood disorders has been called into question (Jimerson et al 1996). With research advances holding out the very real promise for enhancing efforts to characterize brain function and process at the molecular level, the not too distant may yield precise reformulations of models of how neurobiological perturbations related to malnutrition act in concert with risk factors of primary pathophysiological relevance to initiate, and then sustain, in more or less autonomous fashion, the core behavioral manifestations of AN and BN.

Molecular Genetics and Heritability

Recent family and twin data, that implicate heritable factors in eating disorders (Lilenfeld et al 1997), have given impetus to the search for disease susceptibility genes linked to AN and BN (Collier et al 1997; Enoch et al 1998;

Sorbi et al 1998; Kaye and Strober in press) with the goal of delimiting proximal biological events in the etiopathogenesis of these disorders. In short, a convergence of new research paradigms may give fresh impetus to more hypothesis guided applications of novel pharmacologic compounds whose function and mechanisms of action suggest the potential for specific therapeutic action and superior efficacy in suppressing binge eating or perseverative, obsessively-driven weight and shape-related cognitions.

Treatment Efficacy, Outcome, and Relapse Prevention

A particularly critical practical question is what types and intensities of interventions across sequential phases of treatment are truly optimal and cost effective for longer term management of eating disorders. It is distressingly clear that treatment interventions that may have value in the acute management of AN and BN do not guarantee longer-term maintenance of gains, and may not be optimally effective in prophylaxis. This is reflected in the difficulty of achieving complete remission of illness in BN patients with either psychosocial (Garner et al 1993) or pharmacologic therapies (Walsh et al 1991b), the frequent relapse of BN patients during continuation therapy with antidepressants (Walsh et al 1991b), and the frequency with which AN patients lose weight after hospital discharge, coupled with the protracted course of their full recovery (Strober et al 1997). These issues are of substantial concerns because the treatment of these disorders can be prolonged and costly (McKenzie and Joyce 1992).

Several questions can be extrapolated from these observations. For example, what factors (historical, clinical, and biological) actually differentiate AN and BN patients who achieve full remission during acute treatment from those who remain partially or fully symptomatic? It is not known at present whether or not being fully asymptomatic upon completion of acute therapy in BN patients, or being at a normal body weight for some period of time for AN patients, is facilitative of fuller and more enduring recovery.

Issues currently debated in the long-term treatment of chronic, relapsing illnesses like unipolar and bipolar affective illness may be informative to eating disorders. Unipolar (Keller and Boland 1998) and bipolar affective patients (Coryell et al 1995) who recover and become fully asymptomatic have a lower risk of recurrence compared to patients who improve, but have continuing residual symptoms or breakthroughs of subsyndromal symptoms during prophylaxis treatment. These observations raise the question of whether or not acute and continuation treatments that bring about a sustained remission of symptoms in

eating disorders patients (i.e., total abstinence from bingeing and purging, or reduced drive for thinness and defense of normal body weight) effectively reduce the longer-term cumulative risk of relapse and recurrence, and if so, what mechanisms initiate and maintain the greater durability of symptom control. For example, is there benefit to long-term continuation pharmacotherapy in BN patients who recover although receiving this treatment? Does exposure of BN patients who recover with CBT to continuing 'booster' sessions of this modality reduce risk of relapse? If so, what duration and frequency of exposure to booster CBT is optimal? Do patients who recover on a combination pharmacotherapy and psychosocial treatment regimen require continuation of both modalities to suppress their symptoms? If so, for what duration, or can one of these components be discontinued without a sacrifice in prophylaxis? In light of the difficulty in achieving full remission during acute phase therapy in BN, might greater efficacy be achieved through use of combination pharmacotherapy (e.g., SSRI-tricyclic regimens), at least in certain patients? Does this strategy have an advantage over switching to psychosocial treatment in patients whose initial treatment is exclusively pharmacologic? With AN, does an extended duration of inpatient care in a specialty treatment program, thus permitting a lengthier period of time at normal body weight before discharge, decrease the risk of early relapse into florid illness by allowing for a more sustained normalization of disease promoting biological sequelae of starvation and by enhancing receptivity to psychotherapeutic interventions?

In short, we can envision a new generation of clinical trials in eating disorders that not only compare the acute efficacy of a wider range of treatment strategies than heretofore investigated, but investigate, as well, the comparative efficacy of strategies differing in type and intensity in reducing longer-term risk of relapse and recurrence.

Psychophysiological Vulnerabilities and Illness State

It is possible that many AN and BN patients have difficulty achieving robust improvements during acute treatment because of underlying pathophysiological processes. As noted above, altered serotonergic neurotransmission and behavioral symptoms persist after recovery from AN and BN. Whether such persisting phenomena have etiological relevance, are scars of illness, or are compensatory, adaptational effects, is unknown. Still, an intriguing question is raised as to the possibility that biological phenomena, whether of primary causal significance, or a secondary consequence of pathologic eating behavior, constrain treatment effects or actually promote the development of treatment tolerance. In addition, little is known about the consequence of malnutrition on both

somatic and psychological therapies. In this vein, several authors (Attia et al 1998; Ferguson et al 1999) have argued that SSRIs may have limited utility during acute phase treatment of AN due to reduced availability of plasma tryptophan or the effects on serotonin gene expression of low circulating levels of gonadal steroids.

Heuristic and clinical paradigms advanced in the study of affective illness may be germane. Although speculative, Post and Weiss (1997) have applied models of kindling and stress sensitization to the study of treatment responsiveness and illness course. They suggest that early and very aggressive therapies may be necessary to abort the unfolding progressive cascade of neurobiological events that may act to promote recurrence and treatment tolerance in cyclical disease processes. This raises questions regarding the possible long-term value of high intensity combination treatments sustained over extended periods of continuation therapy. Admittedly speculative, the arguments advanced by Post and Weiss (1997) are provocative at the very least, and although their relevance to eating disorders is arguable, these concepts underscore the future importance of integrative models of research wherein treatment and behavioral neurobiology are viewed in a dynamic, temporal framework.

Cost of Treatment and the Cost of Failure to Treat

Managed care has produced a substantial reduction in support of the treatment of eating disorders. Although managed care companies seem relatively resistant to arguments that treatments improve quality of life, they may be more open to arguing the cost effectiveness of aggressive treatments early in the course of these illnesses. The high morbidity and mortality of AN in particular (Herzog et al 1992; Sullivan 1995) raises the question of whether failure to adequately treat in the short run is offset by the cost of treating severe medical complications or increased public welfare burden. Moreover, as Koran et al (1995) have noted, it is becoming necessary to consider the cost of treatment when comparing the efficacy of different treatment.

Advocacy Movement and Destigmatization of Eating Disorders

Alliances between research, mental health treatment, and affected people and their families have become increasingly important. For example, alliances between NAMI and NARSAD have been successful in using biologic advances to destigmatize treatment for schizophrenia and argue for parity. The advocacy movement in eating disorders has been a strong and active movement for many years. Still, contemporary treatment, managed care, and legislative issues suggest that certain revolutionary direc-

tions might confer benefits to the eating disorder field. This relates, for example, to increased national presence in terms of legislative lobbying and improved collaborations between research and families to destigmatize eating disorders.

Conclusions

The difficulties faced by clinicians in the treatment of AN and BN will continue, and may even magnify, as trends in health care delivery reduce access to extended care and treatment in specialty inpatient facilities. These external forces may compromise efforts, at least with respect to more severely ill patients, to suppress behavioral and biological sequelae of illness whose control is fundamental to the longer-term effectiveness of available therapies. Ultimately, the complexities involved in treatment research conducted within broader integrative research paradigms will likely require multi-site collaborations between specialty treatment centers so that talents from a broad array of disciplines can be applied with the greatest possible effectiveness and efficiency.

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