

REVIEW

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# Perplexities of treatment resistance in eating disorders

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## Abstract

**Background:** Treatment resistance is an omnipresent frustration in eating disorders. Attempts to identify the features of this resistance and subsequently develop novel treatments have had modest effects. This selective review examines treatment resistant features expressed in core eating disorder psychopathology, comorbidities and biological features. Novel treatments addressing resistance are discussed.

**Description:** The core eating disorder psychopathology of anorexia nervosa becomes a coping mechanism likely via vulnerable neurobiological features and conditioned learning to deal with life events. Thus it is reinforcing and ego syntonic resulting in resistance to treatment. The severity of core features such as preoccupations with body image, weight, eating and exercising predicts greater resistance to treatment. Bulimia nervosa patients are less resistant to treatment with treatment failure related to greater body image concerns, impulsivity, depression, severe diet restriction and poor social adjustment. For those with binge eating disorder overweight in childhood and high emotional eating predicts treatment resistance. There is suggestive data that a diagnosis of an anxiety disorder and severe perfectionism may confer treatment resistance in anorexia nervosa and substance use disorders or personality disorders with impulse control problems may produce resistance to treatment in bulimia nervosa. Traits such as perfectionism, cognitive inflexibility and negative affect with likely genetic influences may also affect treatment resistance. Pharmacotherapy and novel therapies have been developed to address treatment resistance. Atypical antipsychotic drugs have shown some effect in treatment resistant anorexia nervosa and topiramate and high doses of SSRIs are helpful for treatment of resistant binge eating disorder patients. There are insufficient randomized controlled trials to evaluate the novel psychotherapies which are primarily based on the core psychopathological features of the eating disorders.

**Conclusion:** Treatment resistance in eating disorders is usually predicted by the severity of the core eating disorder psychopathology which develops from an interaction between environmental risk factors with genetic traits and a vulnerable neurobiology. Future investigations of the biological features and neurocircuitry of the core eating disorders psychopathology and behaviors may provide information for more successful treatment interventions.

**Keywords:** Treatment resistance, Anorexia nervosa, Bulimia nervosa, Binge eating disorder

## Introduction

Treatment resistance is a common feature of eating disorders documented by poor response rates in many treatment trials. Studies of predictors of response to treatment have shown varying results depending on eating disorder diagnosis and definitions of response and recovery [1]. A literature search from years 2000 to 2012 using the terms treatment resistance, anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder

(BED), and eating disorders yielded 38 papers from Pub Med and 26 papers from Psych Info. In the overwhelming majority of these papers the term treatment resistance was used interchangeably with chronicity of illness or difficult to treat. There were also multiple definitions of treatment failure including no definition. The author decided not to present a comprehensive review of “treatment resistance” but rather mention those articles with salient relevant features of the author’s interest in three areas; core eating disorder psychopathology, comorbidity, and biological features. A variety of novel psychotherapies addressing “treatment resistance” in AN have

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been developed. All of these need further efficacy and effectiveness trials and are referred to briefly as are some pharmacotherapies for AN. A few treatment studies with adequate sample sizes addressing “resistant” patients with BN and BED are presented along with the author’s suggestions.

## Review

### Core eating disorder psychopathology

Treatment resistance is especially prominent in anorexia nervosa patients who often deny their fear of gaining weight and the seriousness of their illness. Many female adolescents with AN have stated openly they do not wish to develop into a mature female body and are fearful of becoming independent of their family [1]. For many AN becomes a coping mechanism to deal with adverse experiences. It provides an escape from aversive developmental (maturity) issues and distressing life events often of an interpersonal nature. Changing their behavior is an overwhelming and terrifying notion to the anorexia nervosa patient. Certain developmental features are common in anorexia nervosa. The majority of these patients have had a lack of experience to foster personal independence [2]. This has produced a sense of personal ineffectiveness and poor self-esteem. Many of these patients also have a social ineffectiveness, which makes them feel ill at ease in dealing with their peers and with life crises. They often have problems of developmental transitions from the prepubertal state through puberty to a mature adult. Their immaturity and autonomy fears are expressed in the form of refusing to separate from their parents. A plausible hypothesis is that their preoccupations with body image, weight, eating and exercising provide a distraction for dealing with distressing life events. In addition, the behavior of their illness gives them a feeling of control and elevates their self-esteem. The mental changes occurring from severe dieting and emaciation further augment treatment resistance. These symptoms of emotional instability, irritability and loss of concentration make it more difficult for the patient to engage in meaningful psychotherapy that results in behavior change. Severity of core eating disorder psychopathology usually predicts greater resistance to treatment in anorexia nervosa patients [3].

Treatment resistance in bulimia nervosa should be able to be inferred from studies of predictors of therapy response. Unfortunately, different studies have found different sets of predictors both for treatment outcome and for attrition. Predictors identified as statistically significant in one study were not found significant in others. This may be due to several factors including the type of therapy, the mode of delivery (i.e., individual or group format, outpatient or inpatient treatment), and the characteristics of the population of bulimic subjects studied.

Many studies have had too few subjects to reliably identify outcome predictors and the definition of treatment success has varied from abstinence from binge eating and purging to no longer meeting criterion of DSM-IV diagnostic criteria. Pretreatment variables and the methods of assessing treatment outcome have varied among the studies. The fact that bulimia nervosa patients are less resistant to treatment than those with anorexia nervosa is demonstrated by the fact there many more randomized controlled trials for treatment of bulimia nervosa compared with anorexia nervosa, a condition in which few people are willing to enter the trials and when they do the drop-out rate and lack of commitment to treatment is considerably greater. One study of 194 women with bulimia nervosa showed those with the treatment resistance (treatment failure) had greater concerns about shape and had greater impulsivity than those who responded to treatment. Non-responders to the immediate end of treatment were also more likely to have current depression, a lower body mass index indicating severe dietary restriction and poor social adjustment [4].

The problem of different studies showing contradictory results for predictors of treatment resistance in BN is present as well as in BED. One study with a large sample of 144 individuals with binge eating disorder found a history of overweight during childhood and high emotional eating were predictors of treatment resistance [5]. In two recent studies severity of body image disturbance and shape concerns were related to treatment compliance and resistance [6,7].

### Psychiatric and psychological comorbidity

Studies presented in this section were chosen for large sample size or the mention of specific traits or concepts. The most comprehensive psychiatric comorbidity study is from the U.S. National Survey Replication [8]. In this study at least one lifetime comorbid psychiatric DSM-IV disorder was present in 56.2% of anorexia nervosa participants, 94.5% of those with bulimia nervosa, 78.9% of those with binge eating disorder, 63.6% with sub threshold binge eating disorder, and 76.5% with any binge eating. Affective disorders which are the most prevalent of the comorbid psychiatric disorders associated with eating disorder were not shown to influence the long term outcome response to treatment in bulimia nervosa [9] or to effect treatment acceptance or completion in anorexia nervosa [3]. The rates of anxiety disorders were similar in 97 individuals with anorexia nervosa, 282 with bulimia nervosa and 293 with anorexia nervosa binge-purge subtype in a large genetic study [10]. Two-thirds of the participants in this study reported one or more anxiety disorders in their lifetime with the most common diagnosis being obsessive-compulsive disorder, 41% and social phobia, 20%. In the majority of these patients

the onset of anxiety disorders occurred in childhood before the emergence of their eating disorder. In this study those individuals who had a lifetime diagnosis of an anxiety disorder and were currently ill with an eating disorder had more symptoms of anxiety, harm avoidance, obsessionality and perfectionism suggesting that a diagnosis of anxiety disorder and more severe symptoms of the traits mentioned may confer treatment resistance. Substance use disorders (alcohol and or drug) occur in 40 to 50 percent of disorders with binge eating. In these eating disorder subtypes substance use disorders are associated with a high prevalence of major depression, anxiety disorders, and cluster B personality disorders [11]. The high degree of multiple comorbidities with substance use disorders and eating disorders makes it difficult to determine the effect that a substance use disorder may have on treatment resistance. Personality disorders are also highly prevalent in the eating disorder population. In one large comprehensive study [12] 69% of the patients had a least one personality disorder and 31% of the bulimic subgroups had cluster B impulsive disorders of which the most prominent was borderline personality disorder present in 25%. The prevalence of cluster C anxious personality disorders was present in 30% of eating disorder patients and did not vary according to eating disorder subtype. A review of bulimia nervosa studies [13] concluded that personality disorders marked by problems with impulse control were associated with a worse prognosis in these patients and thus suggesting an association with treatment resistance.

There is some indication that personality traits may influence response to treatment and treatment resistance. Perfectionism is a personality trait initially identified with anorexia nervosa. In one study of 322 women with a history of anorexia nervosa greater perfectionism was associated with lower body weight, greater prominence of eating preoccupations and rituals and a diminished motivation to change, the latter implying a greater resistance to treatment [14]. There is an indication that temperament features may also affect responsiveness to treatment in eating disorders. Diagnostic crossover from anorexia nervosa to bulimia nervosa and visa versa in one large sample study was consistently associated with low self-directiveness [15]. There is also a suggestion that the severity of negative affect may influence treatment responsiveness in binge eating disorder [16]. In a study of 74 individuals with eating disorders including anorexia nervosa, bulimia nervosa and eating disorders not otherwise specified, those patients with a combination of low self compassion and high fear of self compassion at baseline had significantly poorer treatment responses [17]. In a response to a stressful speech task, recovering anorectic patients demonstrated greater negative emotional responses compared with controls.

The author suggested that the persistence of a negative affect with distress following recovery may place these patients at risk for relapse and this may also influence anorectic patient's resistance to treatment [18]. Difficulties in cognitive flexibility are characteristics of patients with anorexia nervosa and may account for treatment resistance in these patients [19]. Cognitive remediation therapy has been proposed as an adjunctive treatment for patients with anorexia nervosa. On a scale measuring existential well being anorexia nervosa participants were found to score significantly lower than age matched controls [20]. The author's suggested that anorexia is a coping strategy that provides a sense of meaning and identity. This however may cause more existential anxiety since these individuals would have limited mechanisms for dealing with this anxiety and make them resistant to treatment efforts.

In a treatment study of binge eating disorder those patients who responded to treatment with a behavioral change had the following 6 attributes; 1) they strongly wanted and intended to change for clear, personal reasons, 2) they faced a minimum of obstacles to change, 3) the patient had the requisite skills and self-confidence to make the change, 4) the patient felt positive about the change and believed it would result in meaningful benefits, 5) the patient perceived the change as congruent with self image and social group norms, 6) the patient received encouragement and support to change from valued persons [21].

#### **Biological features**

Considerable evidence for altered brain serotonin and dopamine function from brain imaging is present for AN and BN. Although these alterations have not been shown to be directly related to treatment resistance, there is evidence they are related to psychological and behavioral features whose severity is associated with treatment resistance. For example, serotonin transporter function has been related to extremes of impulse control in BN [22]. A positron emission tomography (PET) study found interactions between D2/D3 receptor and serotonin transporter binding were related to harm avoidance. The latter is a measure of inhibition and anxiety [23]. Another study showed increased serotonin 1A receptor binding in recovered bulimics and this positively correlated to harm avoidance in specific brain areas [24]. A later study showed ill and recovered BN have altered serotonin transporter binding which the authors suggest may influence responses to medication [25].

Psychometric studies have linked AN and BN to a cluster of moderately heritable personality and temperamental traits, such as obsessionality, perfectionism, and harm avoidance [26] A linkage analysis of an AN cohort containing extreme high ratings for drive-for-thinness

and obsessiveness produced a significant linkage at 1q31.1 for those covariates. The allele frequency differences in the GABA receptor SNP, GABRG<sub>1</sub> was found to be related to levels of trait anxiety in anorexia and bulimia nervosa probands. High anxiety levels are characteristic and present to a greater degree in persistently ill eating disorder probands compared with those who have recovered. Thus, this GABA receptor aberration may be related to treatment resistance [27]. In a study of behavioral profiles of anorexia nervosa probands and their parents, a class was identified of probands with mother – daughter symptom severity for eating disorder psychopathology and anxious/perfectionistic traits. It could be hypothesized that these probands may have a genetic propensity for treatment resistance [28].

### Efforts at treating refractory patients

The literature on treating refractory patients consists mainly of suggestions based on observations of patients. These studies are mostly uncontrolled and with small samples. Over the past 20 years eating disorder hospital treatment has changed from long term treatment to stabilization of acute episodes. For treatment resistant patients this change has been deleterious and not cost effective as shown in one study with readmissions changing from 0% to 27% of total admissions [29]. For anorexia nervosa patients contingencies attached to behavioral goals could be changed or the intensity of treatment increased such as residential treatment with a daily structure in careful monitoring to prevent readmissions. At times involuntary hospitalization with enteral feeding may be necessary. Pharmacotherapies that have shown some effectiveness in treating resistant anorexia nervosa include haloperidol [30] quetiapine and olanzapine [31,32] and Duloxetine [33]. Several novel psychotherapies are being developed for treating resistant anorexia nervosa include the following; 1) Cognitive Behavioral Therapy Extended [34]: this focuses on addressing predisposing and maintaining factors of the eating disorder as well as involving caregivers to support the patient with matters regarding food, eating and psychological factors. Cognitive Remediation Therapy was developed to treat an inflexible thinking style [35]. Modest results were obtained. Another 10 session treatment package that primarily addresses emotion processing difficulties in the self and others and includes strategies to manage emotions and the practice of emotion expression has also had modest results. This therapy is called Cognitive Remediation and Emotional Skills Training (CREST) [36]. Maudsley Model for Treatment of Adults with Anorexia Nervosa (MANTRA) is another form of therapy which addresses rigid thinking styles with perfectionism and obsessive compulsive personality traits and the avoidance of strong emotional responses to others. It includes motivational interviewing

and a CBT framework [37]. Community outreach partnership program (COPP) has a goal of improving quality of life and minimizing harm [38]. Specialist supportive clinical management (SSCM) emphasizes support for changes that will improve quality of life as well as physical well being. Its aim is to provide a therapeutic match to the chronic patient's level of ambivalence [39,40]. It does this by allowing flexibility in the approach. Strober [41], advocates a different paradigm in which management replaces traditional objectives of therapy to support the patient in a palliative holding management of carefully measured intensity. Small steps are taken to partially compensate or cushion the effects of the illness. This is done by assuring the patient weight gain will not be a principle objection of the management approach, encouraging the patient to maintain some type of social activity and involvement in hobbies, intellectual pursuits or activities that allow for feelings of pleasure. It also requires regular physical exams and exploring possibilities of improvement in nutrition. In therapy with treatment resistant anorectics Vanderlinden [42], emphasizes the quality of the therapeutic alliance and the timing of therapeutic strategies as well as focusing less on the content of cognitions and more of the emotional involvement with cognitions. He also emphasizes focusing on dysfunctional cognitions and messages within the family communications and interactions.

In treating resistant bulimia nervosa patients sequential treatment is often effective. In one study [43], 20% of non responders to cognitive behavioral therapy responded to fluoxetine or interpersonal therapy at the same rate. Resistant bulimics may require a partial hospitalization or inpatient program for a short period of stabilization. Additional or separate treatment for comorbid diagnoses with bulimia may be indirectly helpful. Examples are alcoholics anonymous for those with substance abuse or dialectal behavior therapy for those with borderline personality disorders. Cue exposure was effectively used to treat resistant adolescents with bulimia nervosa [44]. The authors emphasize that cue exposure prevented the binge itself whereas exposure response therapy prevents post bingeing behaviors and the latter has not been effective in treating resistant bulimics.

For binge eating disorder resistant patients a recommendation is suggested of high doses of SSRIs or the drug topiramate starting at 25 mg daily and increased by 25 mg weekly [45].

### Conclusions

Trait – related multigenic and neurobiological vulnerability when modulated by environmental risk factors influence the development of eating disorders and may also contribute to treatment resistance. These conditions once established are sustained by conditioned learning and state related pathophysiological changes [46]. Since



none of the efforts at treating resistant eating disorder patients have been dramatically effective, future investigations of neurobiological factors and neurocircuitry in eating disorder patients may provide information for more successful treatment interventions.

#### Competing interests

The author has no competing interest.

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