Report of the National Institutes of Health workshop on overcoming barriers to treatment research in anorexia nervosa

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Report of the National Institutes of Health Workshop on Overcoming Barriers to Treatment Research in Anorexia Nervosa

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Accepted 18 August 2003

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Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/eat.10261
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Abstract: Objective: Anorexia nervosa (AN) is associated with serious medical morbidity and has the highest mortality rate of all psychiatric disorders. The National Institutes of Health (NIH) Workshop on Overcoming Barriers to Treatment Research in Anorexia Nervosa convened on September 26–27, 2002 to address the dearth of treatment research in this area. The goals of this workshop were to discuss the stages of illness and illness severity, pharmacologic interventions, psychological interventions, and methodologic considerations.

Method: The program consisted of a series of brief presentations by moderators, each followed by a discussion of the topic by workshop participants, facilitated by the session chair. Results: This report summarizes the major discussions of these sessions and concludes with a set of recommendations related to the development of treatment research in AN based on these findings. Discussion: It is crucial that treatment research in this area be prioritized. © 2004 by Wiley Periodicals, Inc. Int J Eat Disord 35: 509–521, 2004.

Key words: National Institutes of Health; National Institute of Mental Health; workshop; anorexia nervosa; treatment

INTRODUCTION

Anorexia nervosa (AN) is a serious but rare disorder (a point prevalence rate of approximately 0.7%) that leads to substantial morbidity and mortality. Although significant progress has been made in understanding ways to treat other eating disorders, notably bulimia nervosa (BN) and binge eating disorder (BED), the literature on effective treatments for AN is scant. A number of obstacles hinder treatment research in AN, including its overall low incidence, lack of consensus on best treatments, variability of presentation within the patient population based on age and illness factors, high costs of providing treatment, and the complex interaction of medical and psychiatric problems associated with the illness.

On September 26–27, 2002, the National Institutes of Health (NIH) Workshop on Overcoming Barriers to Treatment Research in AN convened in Bethesda, MD. Sixteen scientists conducting research on the causes and treatments of eating disorders participated in the workshop, which was cosponsored by the National Institute of Mental Health (NIMH) and the NIH Office of Rare Diseases (ORD). The four conference sessions focused discussion on areas assumed to be most germane to the dearth of treatment research in AN: stages of illness and illness severity, pharmacologic interventions, psychological interventions, and methodologic considerations. This report summarizes the major discussions of these sessions and concludes with a set of recommendations based on these findings.

SESSION 1: STAGES OF ILLNESS AND ILLNESS SEVERITY

AN is a serious disorder with high mortality rates consequent to both malnutrition and suicide. Adjusted mortality rates range from 1.2% to 12.82% and the suicide rate is 56.9%. The disorder usually commences with pure dietary restriction, but over time such restriction tends to break down, resulting in binge eating and purging in over 50% of the cases. AN is often accompanied by serious comorbid psychopathology, principally depression, anxiety disorders, obsessive-compulsive disorder, personality disorders, and
substance use disorders. There is some evidence that such psychopathology becomes more complex and difficult to treat over time. Although no predictor of outcome is entirely reliable, studies suggest that extreme low weight at presentation predicts poor outcome. By contrast, presentation at early onset of the disorder predicts a better outcome, with a higher recovery rate for patients younger than age 18 than in later years.

AN is also associated with a number of severe medical problems, such as osteopenia and osteoporosis, structural and functional brain changes, potentially lethal cardiovascular complications, fluid and electrolyte changes that are not directly related to frequency of purging, and disturbances in immune functioning. Many of these areas require detailed study. One area in which studies are already underway is in the treatment of AN-related osteoporosis, which affects approximately 38% of individuals with AN. A placebo-controlled trial revealed that low-dose estrogen has no significant effect on bone density. However, a further trial found that insulin-like growth factor-I (IGF-I) is associated with increased bone density and bone mass and that the group receiving both IGF-I and low-dose estrogen shows the greatest gains. These improvements are independent of weight gain. (Notably, the high rate of participation in these trials markedly exceeds participation rates in other psychiatric treatment trials.) Methods of nutritional rehabilitation, medical management of serum electrolyte abnormalities, and other medical complications such as osteopenia and osteoporosis should be further investigated to enhance treatment effectiveness.

In general, primary prevention programs for the eating disorders have not been shown to be particularly effective. Given a low likelihood of developing useful primary prevention programs for AN in the near future (because few risk factors specific to AN have been identified, and such efforts are hampered by the low incidence of the disorder), efforts to improve early recognition and treatment may be more productive approaches.

The heterogeneity of patients with AN in age, chronicity, and severity of psychological symptoms likely contributes to variability in treatment outcomes. It is generally agreed that AN may be usefully divided into acute (roughly adolescent) and chronic (roughly adult) phases. However, it is unclear how to categorize early warning signs or residual symptoms short of recovery. Approximately 20% of cases become chronic and a further 30% experience residual symptoms short of full recovery. Researchers should define study populations accordingly. Data suggest that for AN, like many other illnesses, the shorter the period between the onset of the disorder and initiation of the intervention, the greater the probability of success. The illness is comparably less rooted in younger than older patients and younger patients typically have easier access to family support that may facilitate recovery.

Countries vary widely in the extent of inpatient, partial care, and outpatient care devoted to individuals with AN and minimal data exist that might inform these policies. The high costs of AN reflect the fact that approximately one half of patients with AN require hospitalization, approximately one half receive medication, and almost all receive some form of outpatient psychotherapy. However, the type of treatment received by patients with AN depends more on reimbursement policies than on clinical need. For example, in the United States, short-term hospitalization on medical units to achieve acute nutritional rehabilitation is becoming standard. In Canada, however, long-term hospitalization aimed at weight restoration, together with psychological treatment in a specialized unit, is common. No controlled studies to date provide data confirming which treatment approach or treatment setting (e.g., outpatient, inpatient) is most effective for each stage of the disorder. However, there are suggestive research findings that approaching or achieving normal weight leads to a better outcome for patients with AN than not achieving such weight gains.
Controlled studies addressing the issue of treatment setting are essential. One logical approach is to use a stepped-care model, based on the patient’s presentation, which entails finding an appropriate intensity of treatment based on factors such as motivational status and progress. Other treatment research areas to consider include the identification of more effective relapse-prevention procedures and “booster” treatments for patients in the process of relapse. Treatment trials aimed at relapse prevention are important to avert chronicity.

SESSION 2: PSYCHOPHARMACOLOGIC INTERVENTIONS

Pharmacologic treatment studies for acute AN are quite limited. For acutely ill patients with AN, none of the controlled pharmacotherapy trials have demonstrated the efficacy of medication. Pharmacology trials in AN can be divided into those treating acutely ill patients versus those targeting relapse prevention. Most trials involving acutely ill patients have been conducted in inpatient treatment facilities where multifaceted programs are in place. These trials address the impact of medications (or placebo) when added to standard multifaceted treatment and, therefore, should be viewed as combined treatment trials. Fifteen such trials have been published. The dopamine antagonists pimozide and sulpiride were both studied in placebo-controlled trials and neither was shown to be of benefit. One antidepressant trial using amitriptyline suggested some degree of efficacy, but given the potential cardiac risks of tricyclic antidepressants (TCAs), they are no longer used in this population. A trial using the selective serotonin reuptake inhibitor (SSRI) fluoxetine in low-weight individuals with AN failed to find benefit. Similarly, a trial of lithium failed to find a significant effect on weight gain. The serotonin antagonist cyroheptadine has been studied in several trials. In the largest of these, the drug appeared to have an antidepressant effect and a positive effect on rate of weight gain. However, the results were modest and were only seen in the restricting subtype of AN. Trials of tetrahydrocannabinol and cisapride have been negative, whereas trials of zinc have provided mixed results, with some evidence of improved weight gain and/or improvement in anxiety and depressive symptoms in two trials.

More recently, a number of case reports have been published on patients treated with atypical antipsychotics such as risperidone and olanzapine and a controlled trial of olanzapine is currently underway. These agents may have advantages over the traditional neuroleptics. A single study aimed at relapse prevention found evidence of benefit for fluoxetine compared with placebo and a larger replication trial is currently underway. Therefore, there is interest in the use of atypical neuroleptics in low-weight, treatment-resistant patients and in the use of the SSRI fluoxetine as a relapse prevention strategy, but controlled trials of adequate size are needed.

Evaluating newly developed agents that modulate neurochemical pathways believed to be dysregulated in patients with AN may offer one pathway to more effective treatment. Candidates for evaluation include antagonists of subtypes of central nervous system serotonin receptors (e.g., 5-HT2C receptors) and corticotrophin releasing hormone (CRH) antagonists. A second promising strategy is to use findings from preclinical studies of various neuromodulators with selective effects on eating behavior. For example, neuropeptide-Y (NPY) and the gut-related peptide ghrelin are potent stimulators of feeding behavior, suggesting that NPY or ghrelin agonist drugs might assist in weight restoration of patients with AN. Conversely, preclinical studies have identified a number of neuromodulators that decrease feeding behavior, including leptin and the gut-related...
peptides cholecystokinin (CCK) and peptide YY\textsubscript{3-36}. It is of particular interest that central melanocortin pathways may play an important role in mediating the anorexic effects of serotonin agonist drugs. Therefore, centrally active antagonists of these neuromodulator systems would also represent promising candidates for study in patients with AN. A third approach involves evaluating agents developed for other psychiatric disorders having symptoms in common with or high comorbidity with AN (e.g., depression). An example would be new drugs in development as potential antidepressant agents, such as CRH antagonists. A fourth strategy is to evaluate the efficacy of newly developed psychotropic agents associated with weight gain in preclinical or clinical studies, such as atypical neuroleptics, to stimulate weight.

Research in this area could also be enhanced by the continued development of standardized clinical assessments. It would be useful to find early, surrogate markers of clinical response or nonresponse, such as drug effects, on eating behavior as measured in feeding laboratory studies. Continued research on the pathophysiology of this disorder will also inform trials of new potentially therapeutic agents.

Study of various neuronal systems that modulate feeding and impulse control may also yield clues to new AN treatments. Several centers have documented altered serotonin activity that persists after prolonged normalization of weight, nutrition, and menstrual function. Anxiety, obsessionality, and perfectionism also persist. There is evidence of reduced serotonin activity in ill patients with AN and increased serotonin activity after recovery. Because serotonin has complex and poorly understood interactions with other neurochemical systems, conventional tools provide a distant and simplistic picture of the activity in this system. Powerful new tools, such as a single photon emission computerized tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), are being used effectively to study these systems. Studies fairly consistently show temporal lobe alterations in ill individuals with AN. However, sample sizes have been small and have used inconsistent definitions of subgroups and states of illness. PET studies using 5-HT receptor-specific radioligands suggest an approximate 100% increase in 5HT\textsubscript{1A} receptor activity in ill patients with AN, as well as a persistent increase of 30%-60% in 5HT\textsubscript{1A} receptor activity after recovery from AN. In both states, the increase occurs in both the 5HT\textsubscript{1A} autoreceptor in the raphe nucleus and the postsynaptic 5HT\textsubscript{1A} receptors in cortical-limbic-striatal regions. Data also indicate that 5HT\textsubscript{2A} receptor activity is reduced in patients with AN. Moreover, there is an inverse relation between postsynaptic 5HT\textsubscript{1A} and 5HT\textsubscript{2A} receptor activity in AN. As new serotonin-specific drugs become available, they should be assessed in patients with AN. Drugs that target the 5HT\textsubscript{1A} receptor may be useful for reducing anxiety, satiety, or behavioral overcontrol in AN.

Several other observations should inform future pharmacologic strategies, including the possible role of malnutrition in drug response, and the fact that AN invariably begins during adolescence shortly after puberty. These observations suggest that gonadotropins might trigger the illness.

In summary, future strategies may be dictated by our understanding of the neurochemical pathways that are dysregulated in AN (e.g., CRH antagonists), our growing awareness of various neuromodulator abnormalities in individuals with AN, (e.g., leptin), and our knowledge of agents shown to be effective for other disorders that are highly comorbid with or share symptoms with AN (e.g., antidepressants).

Developmental, social, and biologic processes all appear to influence the onset and course of AN. Recent data underscore the importance of neurobiologic vulnerabilities and the need to identify behavioral or biologic endophenotypes that index liability to AN. Family history
studies show that AN aggregates in the first-degree relatives of people with AN and BN and that greater than 50% of the risk for AN is attributable to additive genetic influences. There is evidence that certain eating disorder symptoms (e.g., binge eating, self-induced vomiting, dietary restraint, and body dissatisfaction) are also moderately to highly heritable. These findings suggest that eating disorders and the continuous traits characteristic of eating disorders are both influenced by additive genetic effects.

Certain behavioral symptoms (e.g., anxiety, obsessionality, perfectionism) are stereotypic in individuals with AN. Identifying these traits (endophenotypes) is important to enrich genetic analyses, as are correlational studies with pathophysiologic findings. It is important to select strategies for identifying risk factors that avoid the confounding effects of malnutrition. Such strategies include assessing risk factors in family members of individuals with AN and characterizing premorbid risk factors or those that persist after recovery. Several behavioral traits meet these criteria, including anxiety, negative mood states, perfectionism, and obsessionality, as well as aberrant body image and eating disturbances.

A better understanding of the behavioral vulnerability traits that influence susceptibility to AN is essential for identifying the responsible genes. However, many of the instruments used to assess vulnerability traits have been borrowed from other disciplines. The eating disorders field needs to develop or refine instruments to define the unique characteristics of AN, as well as measures that are performance based, and perhaps neurophysiologically based, including those reflecting regional activity that would correlate with brain-imaging results.

SESSION 3: PSYCHOLOGICAL INTERVENTIONS

As with pharmacologic AN research, psychotherapy studies of AN are remarkably small in number, with fewer than a dozen published controlled outpatient treatment trials. Samples sizes are typically small and, to date, no multisite trial has been published. Attrition is quite high, raising concern about the validity of the findings. The studies published on treatment outcome of AN are also underpowered and have many other limitations. Of the nine published randomized controlled trials (RCT) of psychosocial treatments for AN, only a few were guided by rigorous protocols. Eight trials were conducted in the United Kingdom and only one in the United States. As of this writing, one completed trial from New Zealand is under review and four additional trials are nearing completion (two in the United States and two in the United Kingdom). The total number of clinical trials is extremely low in comparison to trials for other major psychiatric disorders, including BN and BED. Only one study has published the treatment manual of the intervention tested. Fidelity of and adherence to treatment are not measured systematically in most studies. There is considerable variability in assessment protocols and the outcome measures do not fully capture the core psychopathology of AN. Some studies have relied solely on questionnaire assessments rather than on the more reliable diagnostic interview method.

Patients who complete treatment, particularly adult and chronic patients, often show only modest benefits. For a substantial number of patients, the treatment response is poor. When treatment effects are found, the “stronger” treatment often outperformed a comparison treatment having no discernible theoretic or clinical rationale and which would not be deemed adequate by eating disorders specialists (e.g., nutritional counseling in the absence of any additional therapy). Some of the treatments with relatively
encouraging results, such as family therapy, are typically only effective for the subgroup of young, recent-onset patients. Finally, results vary considerably across studies so that apparently similar techniques provide highly conflicting findings, even with seemingly similar patients.

The current literature may better suggest which treatments to avoid than which to adopt. Evidence suggests that for adult patients, treatments that are very limited in time (20 sessions or less), or that consist solely of medication or nutritional counseling, are not effective. Indeed, the relatively modest success of specific interventions in adult patients may reflect delivery of truncated or attenuated treatments and/or insufficient regard to the particular nature of AN or issues of chronicity more than it reflects the impact of any particular treatment paradigm (e.g., family systems theory; cognitive-behavioral theory).

Although the treatment literature has not yet identified effective treatments for AN, there are reasons for optimism concerning the long-term success of psychotherapy research in this area. First, in follow-up studies of patients with AN, approximately 50% recover, 25%-30% improve, and 15%-20% have intractable and persistent illnesses or eventually die due to complications arising from the disorder. However, it is unclear what the role of treatment is in recovery of AN. Also, most patients show symptomatic improvement while in treatment, a potential starting point for the design of newer and more effective interventions. Further, examining which factors contribute to recovery may point to effective treatment strategies. Second, many studies have significant methodologic limitations that compromise their conclusions, including the conclusion of treatment failure. Improved methodologies may result in better outcomes. Third, treatment approaches have paid insufficient attention to some of the distinctive features of AN that may contribute to poor treatment outcome. Specifically, the nature of the symptoms (e.g., pride, competitiveness, and moral certitude) typical of individuals with AN is not addressed in detail in the empirically evaluated treatments to date. Greater appreciation of the inherent difficulties in such efforts may temper the sense of frustration clinicians often experience in working with this population and may suggest additional treatment emphases to improve treatment efficacy.

Several treatments found to be effective with other eating disorders (e.g., BN, BED) should be considered for potential application to patients with AN. First among these would be CBT. This form of treatment has been used extensively with BN patients, but only one small trial of CBT for AN has been published. Next, interpersonal psychotherapy (IPT), which has been helpful for BN and a variety of related disorders, should be further evaluated. For younger patients, family-based treatments appear to be promising and in need of further evaluation. Carefully designed studies are required to clarify how patient age and duration of illness affect outcome and how these parameters influence treatment selection. Further, the often-confounded effects of age and illness duration need to be separated.

To improve treatment studies, the development of standardized treatments needs to be based on a clearly articulated theoretic foundation or clinical dimension (e.g., external control vs. emphasis on autonomy and personal decision-making and direct vs. indirect efforts to alter patients’ positive valuation of symptoms). Studies should be manual based, with adherence measures used and evaluated as part of the research. In addition, it is critical to develop credible control or comparison groups. This may involve use of an active treatment with a different mode of action and no overlapping therapeutic ingredients. Alternatively, a comparison group may involve less psychotherapeutically active treatments (e.g., medical support and oversight or “usual care”). Equally important is the use of a standard assessment protocol to aid in comparing results across studies. Such a
protocol must be suitable for measuring comprehensively the psychopathology of AN and for capturing the major health and mental health outcomes.

Given the obstacles inherent in designing and completing treatment studies of AN, it is essential that investigations have sufficient statistical power to detect differences between treatments. Novel strategies should be developed to minimize drop-out and improve patient adherence. In addition, because we know little about which patient characteristics might affect treatment response, studies should include moderator analyses. Once a treatment appears promising in preliminary investigations, we can then investigate mediators of treatment outcome and identify operative mechanisms of the effective treatments. Finally, it is imperative to support pilot studies of novel treatments in addition to more in-depth investigations of more established approaches.

SESSION 4: METHODOLOGIC CONSIDERATIONS

Economic, social, and attitudinal patient and staff factors all impede optimal AN treatment. Even if there were clear evidence-based guidelines for treating AN, barriers to their implementation would still exist. These factors must be considered in planning and designing treatment research studies and disseminating their results.

A major economic barrier stems from widespread lack of appreciation for the extent of disability caused by AN. This is reflected in restrictive policies at the state and hospital level that limit length of stay or allowable outpatient visits. These restrictions have led to efforts to minimize inpatient stays and to replace inpatient time with extended day-patient options. However, there are no data to support shorter hospital stays coupled with extended day-patient programs as an effective alternative to inpatient stays.

The key social/attitudinal barrier affecting treatment is a pervasive pessimism about the potential for change in patients with eating disorders. Despite progress in understanding the biologic and genetic underpinnings of these disorders as well as preliminary data suggesting that if treated early the majority of patients do recover, the perception remains that these are untreatable, self-imposed disorders. These uninformed attitudes influence policy and resource decision-making at multiple administrative levels. Patient factors also hinder treatment. The nature of AN symptoms (e.g., denial of illness, difficulty establishing trust, and lack of motivation to change) challenges both researchers and clinicians. Improved therapeutic strategies for overcoming these barriers are worthy of additional study.

Finally, staff factors are apparent in both treatment and research settings. The perception of AN as a “difficult disorder” to treat may sway some career decisions into other fields. Limited availability of training opportunities for young clinicians and investigators may also dissuade promising young investigators from choosing this field of study, as may the perception of limited availability of federal funding for eating disorders research.

Services research needs to be directed towards understanding the impact of current treatment trends in the community. For example, the efficacy of longer inpatient hospitalizations compared with shorter inpatient stays followed by extended day-patient care should be addressed empirically, as should the impact of the attenuated weight gain associated with shorter inpatient stays on outcome and recidivism. Similarly, studies need to examine for whom partial hospitalization, intensive outpatient, or traditional outpatient care are reasonable and safe alternatives to inpatient care. In addition, active attempts should be made to disseminate an accurate view of eating disorders as complex and sometimes fatal psychiatric disorders, as opposed to self-imposed conditions. Rather
than dismissing patients with AN as nonadherent and difficult to treat, additional research is required to understand factors that contribute to nonadherence and to develop strategies for enhancing motivation to change. This information should be disseminated broadly wherever policy is influenced, from the federal, to the state, to the individual institutional level.

Currently, the majority of efficacy studies have been small, brief, marked by substantial drop-out, and with minimal long-term follow up. In general, clinical studies have utilized single interventions rather than the spectrum-of-care approach most commonly used in the field. Empirical data are needed to support existing spectrum-of-care treatments. Importantly, justification is required for resource-intensive treatment. The development of novel therapies and pharmacologic treatments should be encouraged. Testing different manualized treatment modalities or combinations of treatments, (e.g., inpatient vs. outpatient, medication vs. psychosocial treatments, or combined treatments) is essential to advance the field. Because AN has far reaching consequences, outcome measures should include—in addition to the core behavioral and cognitive features—quality of life, social adaptation, and resource utilization.

Given the low base rate of AN, recruiting adequate numbers of patients for treatment studies is often a significant challenge. This difficulty is compounded by the nature of AN symptoms and the reluctance of some individuals to seek and accept treatment. A total of 468 patients participated in nine published RCT psychotherapy trials, which averaged 52 subjects per study or approximately 15 individuals per treatment cell. Small cell sizes have seriously limited statistical power to detect meaningful differences across treatment groups. Given the difficulties of recruitment, investigators are often forced to compromise their target cell sizes or elongate their recruitment interval. Several investigators described a recruitment pattern of early success (when many untreated individuals exist in the community from a wide range of cohorts) followed by a rapid diminution of available new cases for entry into the study. At the point of diminishing returns, waiting for incident cases for recruitment becomes financially and logistically unviable. This pattern suggests that multisite investigations could take advantage of the large pool of untreated individuals across several geographic areas and avoid the diminishing returns associated with prolonged recruitment in one area.

Once individuals are recruited into studies, retention varies somewhat according to the age of the sample recruited. Among adolescent participants, the drop-out rate is approximately 10%, but this range increases to 13%–66% for adult samples. This pattern of retention encourages early detection and intervention. Additional work should explore patient and parent variables that influence drop-out. Creative strategies for retention should be explored, including the enlistment of auxiliary individuals such as parents, school counselors, coaches, and potentially, peers.

The overwhelming majority of participants in the published trials have been Caucasian females, which in part reflects the relative ethnic homogeneity of the United Kingdom (where 90% of these studies have been conducted) and the gender ratio for AN. However, it may also reflect a truly lower prevalence of AN among minorities. Data are not yet available to determine whether specific adaptations are required in AN treatment for ethnic minorities or men. Additional clarifying studies are required to determine whether symptom expression in these disorders differs by culture and gender.

Strategies should be developed to assess the magnitude of treatment needed in ethnic minority populations and in males. Strategies should also be developed for improving the recruitment of ethnic minorities and assessing treatment acceptability. Efforts to retain ethnic minorities should include strategies such as weekly contact calls, multiple
incentives for participation, and the participation of peer leaders from the community to aid program promotion. The inclusion of culturally competent consultants on research teams would aid in the development of these strategies.

Lessons learned from the treatment of related disorders may be applicable to research on AN. Early behavior change in treatment predicts outcome with BN and many other disorders. The extent to which change reflects fixed temperamental or motivational features is unclear. Whether it is a function of modifiable individual factors should be investigated.

Additional research is required to understand factors that contribute to maintaining anorexic behavior, such as perfectionism, inflexibility, mood intolerance, and core low self-esteem. These traits may be modifiable and important intervention targets and may contribute to poor outcome. Few data now suggest how best to address comorbidity in individuals with eating disorders (due, in part, to type exclusion criteria in many clinical trials). With mood disorders, anxiety disorders, and substance use disorders becoming increasingly common, this question urgently requires an answer. Outcome measures of clinical trials for AN should include both measures of core and associated symptoms as well as measures of quality of life, social adaptation, and resource utilization.

The study of adolescent samples is particularly important because early intervention is associated with better outcome. In addition, studies should not be limited to narrowly defined samples of individuals with AN as defined by criteria in the 4th ed. of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994). Using such patient groups will hinder identifying predictors of treatment outcome and differential treatment needs. Criteria such as amenorrhea and body image distortion are not universally observed. Broadening the diagnostic criteria would permit more productive exploration of the nature and variations of AN. Understanding the course of illness, outcome, and differential treatment needs requires studying broader samples of individuals. Broader—and hence larger—samples would also increase statistical power.

Strict adherence to the DSM-IV diagnostic criteria for entry into clinical trials has also hampered research on the course, nature, and outcome of the illness. A broadening of diagnostic criteria would enable exploration of the boundaries of the illness and predictors of treatment response in less homogenous groups and would assist with determinations of treatment selection based on patient factors. The current diagnostic criteria are somewhat arbitrary and disallow a number of patients who clearly would meet all but weight and/or menstrual criteria for the disorder. Some patients who do not meet all diagnostic criteria are in the early stage of the illness and early intervention (i.e., before all criteria are fulfilled) may result in better outcome. The overlap between BN and AN symptoms also requires further investigation, due to the reported differences among subgroups by age, subtype, and duration of illness. In an efficacy study, an understanding of the impact of these types of variations in subjects would suggest that subgroups of patients be analyzed separately for differential responses. In effectiveness studies, although these are somewhat lesser problems, researchers still need to be clear about the population under investigation.

**SUMMARY RECOMMENDATIONS**

There is a pressing need to improve early recognition of AN to facilitate early treatment when outcomes are more favorable. Effective methods of dissemination of accurate
information about AN to primary healthcare providers and therapists should be explored. In addition, large-scale pharmacologic intervention studies for AN focusing on resolution of primary psychological symptoms, weight restoration, and relapse prevention must be pursued. Atypical neuroleptics and SSRIs are promising agents for these investigations. New methods for identifying, preventing, and treating the adverse medical consequences of AN are also needed.

Large-scale psychological intervention studies for AN must be encouraged. To date, family therapy for adolescents and CBT for adults are promising and intervention studies aimed at relapse prevention in chronic AN patients are warranted. Overall, there is a need to support innovative treatment and pilot research efforts to guide larger-scale intervention studies. Studies showing how treatment settings affect outcome in patients with AN are needed as well.

Treatment intervention studies should include an adequate sample size (power), standardized assessments and treatments, and credible comparison conditions. In addition, outcomes should assess quality of life, social adaptation, and cost of care. These aims can only be achieved through multisite trials.

The study of moderation and mediation of treatment outcomes should be encouraged in all intervention studies as either primary or secondary research questions. Treatment studies should be encouraged to use clinically meaningful diagnoses rather than strict DSM-IV criteria for AN to better explore the course, nature, and outcome of AN. Studies should include strategies to reduce drop-out rates, assess patient motivation for treatment, and improve adherence, and should include ethnic minorities and males.

Finally, abnormalities in the neurochemical pathways that are dysregulated in AN need to be further explored to promote the development of novel pharmacotherapies. Development of psychological treatment for AN should be encouraged, as only a small number of therapies are currently in use or under investigation. These treatments should be articulated in theoretic or clinical dimensions (e.g., external control vs. autonomy and direct or indirect efforts to alter behaviors and attitudes).

**CONCLUSIONS**

AN is a severe psychiatric illness that leads to substantial morbidity and mortality. Still, an extremely limited amount of research exists on effective treatments for this disabling disorder. To advance the field in identifying and disseminating effective interventions for AN, it is crucial that treatment research in this area be prioritized.

The authors thank Natalie Coutu for her assistance in the preparation of this article.

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