November 3, 2017

Comparative Effectiveness of Outpatient Treatments for Adolescents with Eating Disorders

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Introduction

Eating disorders are characterized by a "persistent disturbance of eating that impairs health or psychosocial functioning".[1] Relevant behaviors include restriction of caloric intake, overeating with loss of control, and compensatory behaviors (e.g., vomiting, exercise, laxative abuse) accompanied by cognitive disturbances, emotional triggers and social difficulties.[2] Eating disorders include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder, avoidant/restrictive food intake disorder, pica, rumination disorder, and eating disorders not otherwise specified (EDNOS). At least 30 million people in the United States will suffer from an eating disorder in their lifetime.[3, 4] Not only are eating disorders prevalent, but they also are sometimes fatal.[2] The scope of this summary is limited to anorexia nervosa (AN) and bulimia nervosa (BN) among adolescents (individuals under 18 years of age). Where evidence is limited in individuals under 18 years of age, studies in adults are mentioned.

Current PCORI Portfolio on Eating Disorders

PCORI has not yet funded research projects that focus on eating disorders. In August 2016, the American Benefit Council suggested that PCORI examine the comparative effectiveness of interventions for eating disorders, with an eye towards comparisons that are outpatient-based and may prevent inpatient treatment.

Methods

Literature search:

We conducted a literature search to identify reports on the treatment of eating disorders. We searched the Cochrane Database of Systematic Reviews, the Agency for Healthcare Research and Quality's website, and PubMed for recent systematic reviews. We also searched websites of the Centers for Disease Control and Prevention(CDC), the National Institutes of Health (NIH), and relevant professional associations and societies (i.e. the UK National Institute for Health and Care Excellence, The American Psychology Association, American Academy of Child and Adolescent Psychiatry, and the American Association of Family Practitioners) for practice guidelines and reports that contain data on the disease burden and impact of the condition on the population.

Ongoing studies:

To identify research that is underway but not completed, we searched ClinicalTrials.gov on October 4, 2017. We used the broad search terms "eating disorder" as well as the specific eating disorder conditions ("anorexia nervosa", and "bulimia nervosa"), "outpatient "and "adolescents".

Summary of Current Evidence

Treatment strategies for eating disorders usually are multidisciplinary (physical, psychological, psychosocial, developmental, and family) with care coordinated across relevant specialists (psychiatrists, dieticians, occupational therapists) and the primary care provider.[5] Unfortunately, there is a lack of high quality empirical evidence that defines the sufficient components of an outpatient treatment program, especially for individuals younger than 18. Additional research is needed to define when each treatment component may have its greatest impact throughout the disease course. Moreover, additional evidence is needed on the types of providers/health care teams that need to be involved in delivering the services and what health service approach is most effective for which patients. A recent shift from inpatient-based to outpatient treatments for individuals who are considered medically stable has enhanced the need for better evidence. Most of the systematic reviews to date have suggested that the evidence is of low to very low quality [5, 6], primarily due to poor study design (lack of blinding, poorly defined outcomes), small sample sizes, insufficient number of CER studies, and inadequate reporting of results.[7]

Anorexia Nervosa

Definition[1]

The latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was released in May 2013. The DSM-5 criteria for Anorexia Nervosa include:

- Persistent restriction of energy intake leading to significantly low body weight (in context of what is minimally expected for age, sex, developmental trajectory, and physical health).
- Either an intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain (even though significantly low weight).
- Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Subtypes:

Restricting type
Binge-eating/purging type

Impact/Burden of Anorexia Nervosa

Most patients diagnosed with AN are female. Age-adjusted incidence rates among U.S. females with AN between 1935-1984 was 14.6 per 100,000 person-years and for males was 1.8 per 100,000. [8] Although incidence rates have been reported to be increasing among U.S. female adolescents aged 15-19y in the last half century [8], other reports in the Netherlands and the UK have reported rates over the last few decades as stable. [8, 10]Lifetime prevalence of AN among adolescents (13-18y) has been reported at 0.3-0.5%.[11]

AN is associated with both short and long-term morbidity. Among children or young adolescents with AN, growth and developmental delays due to malnutrition have been reported.[13] Long-term sequelae such as osteoporosis and increased risk of bone fractures later in life have also been well documented. [13] Evidence suggests that 20% of patients with AN develop a chronic eating disorder [14], some of which may crossover to BN. [15]

Mortality rates associated with AN are not only the highest among all eating disorders but also higher than any other psychiatric disorder.[15, 16] The crude mortality rate for AN is 5.6% [16] with 1 in 5 deaths due to suicide.[15] The highest rate of premature death among patients with lifetime AN occurs within the first 10 years of a diagnosis and is more common among patients with the longest duration of the illness, highlighting the importance of early diagnosis and intervention.[17] Mortality rates tend to be highest among individuals with AN and a psychiatric co-morbidity.[17]

Risk factors

Gender: AN is up to 10 times as common in women as in men.[5] Among U.S. adolescents, girls report having AN 2-3 times more often than boys.[11]
Age: Incidence rates are highest in adolescents (age 15-19)[9], with a median age of onset among U.S. adults at 18 years of age.[19] The median age of self-reported onset among U.S adolescents (12-18y) is 12.3 years.[11]
Family history: Monozygotic twins are more likely to be concordant with AN than dizygotic twins and AN tends to cluster in families.[20, 21]
Co-morbid condition: One third to more than half of adolescents with AN report having a comorbid mood disorder (i.e., depression) and/or a comorbid anxiety disorder (i.e., OCD, social phobia).
Race/Ethnicity: Among a nationally representative sample of U.S. adolescents, non-Hispanic white adolescents were more likely to report AN than adolescents of other race or ethnicities.[11]

Guidelines for the Treatment of Anorexia Nervosa (see Table 1)

- Treatment of anorexia nervosa is typically offered as outpatient care for medically stable individuals.
- Refeeding is a critical component of treatment, but is not sufficient.[14]
- Family-based therapy (FBT) is recommended as first line therapy for children and adolescents with anorexia nervosa. [1,2]
- Pharmacotherapy should not be utilized as a sole treatment strategy. [1, 2]

Current Evidence

Psychotherapy

- A Cochrane systematic review of 13 trials reported on evidence from two trials that demonstrated efficacy of family-based therapy (FBT) in improving remission rates relative to standard of care.[7] The evidence on the efficacy of FBT in the long-term is limited with most studies evaluating outcomes at end-of-treatment or with limited follow-up (6 months-1 year).[7]
- Growing evidence suggests that FBT, or the Maudsley method, may be most effective among adolescents. [2] One trial comparing FBT to other psychological interventions reported a statistically significant increase in rate of remission, % average body weight, and improvement in cognitive distortions among a subgroup of adolescents under age 18 with an illness duration of less than 3 years.[7] No significant differences were seen in similarly conducted head-to-head trials conducted among adults.[7]
- A Cochrane systematic review of 10 trials reported some evidence of efficacy of individual psychological therapy and suggested head-to-head comparisons were of very low quality. [5] Few studies comparing individual psychological therapies have been done exclusively among adolescents.
- **Limitations**: Studies were limited in number and sample size (most <60 individuals) with no or short duration of follow-up, and selective reporting that may have led to bias.[7] Evidence was generally regarded as low to very-low quality. [5,7]
- **Evidence Gaps**: For children, adolescents, and young adults with AN, insufficient evidence is available on:
    - The optimal type or form of FBT
    - Effectiveness of FBT compared to other psychological interventions
    - Long-term effectiveness of FBT on remission rates
    - Effectiveness of FBT and other psychological interventions addressing a full range of outcomes including general functioning and family functioning

Medication

- Antidepressants compared to placebo have not been shown to improve weight gain or psychopathology in adults with acute AN [6]. Few studies have evaluated antidepressants in adolescents (12-18y).
- Efficacy of antipsychotics (e.g. olanzapine, risperdone) have not been shown to differ from placebo on outcomes such as weight, BMI, and self-reported outcomes including depression and anxiety.[24]
- In weight-restored patients, fluoxetine lowers risk for relapse and has been associated with weight maintenance and fewer symptoms of depression.[6, 27, 28] When fluoxetine was added to CBT among weight restored patients, however, the combined treatment did not decrease the risk of relapse beyond what was achieved by CBT alone. [27, 28]
- **Limitations**: These studies were severely limited by sample size (< 60 patients in total), short duration of intervention with no or limited follow-up (<12 weeks), and lack of information on adherence.[6]

- **Evidence Gap**: Lack of efficacy of medications limits ability to conduct CER, particularly among adolescents.

Carer Interventions

- Interventions directed at the carer (self-help books, guided self-help, online services, and workshops) improved carer distress, burden and expressed emotion according to a meta-analysis of 13 studies.[31]
- **Limitations**: Few RCTs have been conducted comparing different types of carer interventions.
- **Evidence Gap**: Insufficient evidence on carer interventions to determine:
    - Optimal interventions for caregiver/carer to reduce carer stress/burden and improve family functioning. Few studies have evaluated whether reduction in carer stress and burden impact patient's well-being.[31]

Delivery of services

- Outpatient treatment is the preferred setting for medically stable individuals based on guidelines, although, systematic reviews of treatment setting have provided inconsistent results due to methodological limitations.
- One of the largest studies conducted among adolescents with AN (12-18Y) comparing treatment settings demonstrated no difference in the Morgan-Russell Scale (quantitative scale assesses weight restoration, menstruation, and absence of BN) among individuals randomized to inpatient versus outpatient programs in a population-based multi-center RCT (n=215) conducted in England.[32]
- No difference in weight and self-reported psychopathology was observed when comparing adolescents who were randomized to a specialist-led multidisciplinary program that incorporated CBT compared to a multidisciplinary program that provided some therapeutic and family-based support delivered by non-specialists in community clinics. Adherence and satisfaction were higher, however, for the specialist-led versus non-specialist led care. [32]
- Stepped care, where patients are introduced to increasingly more intensive care based on lack of response to initial less-intensive interventions, can be difficult to implement with patients who have AN. Early indicators for additional intensive treatment are difficult to identify in patients with AN.[26]
- **Limitations**: Few comparative effectiveness studies have evaluated the level of intensity (particularly for outpatient care) and long-term impact of different treatment settings based on specific patient characteristics.
- **Evidence Gaps**: Additional CER is needed to compare:
    - Key components and combinations of multidisciplinary outpatient care.
    - Level of intensity of outpatient care relative to partial hospitalization and in-patient care
    - Most appropriate early indicators to be utilized for stepped care

Ongoing Research

ClinicalTrials.gov results

We searched clinicaltrials.gov on October 4, 2017. A total of 57 studies concerning "anorexia nervosa" were found. We narrowed our search to 'outpatient' treatments and found that 46 studies were removed, leaving 11 studies specifically testing outpatient treatments. Six studies included patients with AN only, while five studies evaluated interventions that were directed at patients with AN as well as patients with other eating disorder conditions. Only 5 of the 11 studies included adolescents.

Of the 11 studies: 8 were randomized trials, 2 were single assignments and one was an observational cohort. Most trials were open label Phase 2 efficacy studies of medication (atypical antipsychotic drugs--olanzapine), transcranial direct current or magnetic stimulation or variations of psychotherapy strategies (e.g., CBT). Five of the 11 studies provided a head-to-head comparison of treatment settings (e.g. stepped care versus inpatient), psychological interventions (with and without medication) or anti-psychotic medications (by type), although the sample size was less than 60 participants for all studies but one. Most trials identified weight or change in BMI as a primary outcome, few studies evaluated other patient-centered outcomes such as general functioning or other psychological outcomes.

We performed a second new search for anorexia nervosa narrowing the search term to "adolescents" and only studies that were recruiting, not yet recruiting, active, not recruiting, enrolling by invitation. We identified 15 ongoing studies, 3 of which were removed because the study sample included hospitalized patients only. Of the remaining 12 that were adolescent-specific, many studies were not randomized or treatment-specific (rather were observational and focused on microbiome, bone mass, or used qualitative methodology) or Phase 2 studies. One study (NCT03097874), however, was conducting a head-to-head comparison of FBT v. FBT plus intensive parental counseling using a stepped care approach (n=150).

Details of these trials can be found in Appendices 1 and 3.

Bulimia Nervosa (BN):

Overview

Bulimia Nervosa, commonly referred to as bulimia is a serious life-threatening eating disorder characterized by frequent and repetitive episodes of binge eating, purging, and feeling of lack of control over these episodes. [4]

Definition[1]

The DSM-5 Criteria for BN include:

- Recurrent episodes of binge eating
  1. Eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
  2. A sense of lack of control over eating during the episode.
- Recurrent inappropriate compensatory behavior in order to prevent weight gain
- At least once a week for 3 months.
- Self-evaluation is unduly influenced by body shape and weight.

BN can be characterized in two ways: purging BN and nonpurging BN.[1] Purging BN refers to regularly self-induced vomiting or misuse of laxatives, diuretics or enemas after bingeing. Nonpurging BN refers to the use of other methods to rid one's self of calories and prevent weight gain, such as fasting, strict dieting or excessive exercise. [1]

Impact/Burden of Bulimia Nervosa

The lifetime prevalence of BN in the U.S. is 1.5% in women and 0.5% in men.[3, 34] A study by Crow and colleagues, found the mortality rates for BN to be 3.9% coupled with a high suicide rate. [29]Compared to other eating disorders, people with BN usually maintain a normal or healthy weight.[1] But like people with anorexia nervosa, they often fear gaining weight, want desperately to lose weight, and are intensely unhappy with their body size and shape.[1] Signs and symptoms of BN center on the preoccupation with weight and body shape and include chronically inflamed and sore throat, swollen salivary glands in the neck and jaw area, worn tooth enamel, acid reflux disorder and other gastrointestinal problems, intestinal distress and irritation from laxative abuse, severe dehydration from purging of fluids, and electrolyte imbalances.[39, 40]

Risk Factors

- **Gender**: BN is more common in U.S. women than men. However, the risk is increased in men who participate in sports. [13]
- **Age**: BN appears to be affecting people at younger ages, and the average age of onset is in late adolescence but rarely diagnosed in children and young adolescents.[31]
- **Family History**: Having a mother or sister with BN are associated with increased risk. [42] Like AN, higher concordance rates were found in monozygotic twins than in dizygotic twins with heritability threshold estimates ranging from 60% to 83%. [21, 43]
- ***Co-morbid condition*.** Psychiatric co-morbidities are much higher in BN than AN. A recent study found a lifetime psychiatric comorbidity rate of 88%, with most of the adolescents having at least one comorbid psychiatric illness. [11]
- ***Environmental triggers.*** Posttraumatic stress disorder, abuse, and impulsive personality traits have also been suggested to be risk factors for BN. Traumatic events like rape, as well as stressors, such as starting a new job, can trigger BN. [32]

Guidelines for the Treatment of Bulimia Nervosa

The American Psychology Association (APA) Guideline Watch (August 2012): Practice Guidelines for the Treatment of Patients with Eating Disorder reviewed new evidence and developments since the 2006 guideline. The 2012 APA guideline found that, by and large, the 2006 guideline had remained correct and current in its recommendations. In 2014, the American Academy of Child and Adolescent Psychiatry (AACAP) published their "Practice Parameter for the Assessment and Treatment of Children and Adolescents with Eating Disorder. The National Institute for Health and Care Excellence (NICE) last published a clinical guideline on the management of eating disorders in May 2017.

The NICE guidelines reaffirm the recommendations of the APA and AACAP that outpatient treatment should always be the first treatment choice. While all three guidelines recommend the use of a nutritionist/dietician, AACAP doesn't recommend nutritional counseling as a sole treatment. See Table 2 for more details.

Current Evidence

Psychotherapy

- The efficacy of psychotherapy in reducing bulimic symptom severity is supported by systematic reviews: CBT, and particularly CBT-BN, has established efficacy (Hay et al, 2009) and is the "treatment of choice" for bulimia nervosa. [2, 24] CBT had more studies supporting it, and on direct comparison with control therapies, there were trends for CBT to be superior. An enhanced version of CBT (that incorporates attention to additional psychopathologies such as mood intolerance, clinical perfectionism, interpersonal difficulties and low self-esteem) has also been shown to be effective at improving the eating disorder examination score among adults with bulimia.[39] CBT was noted to be the only psychotherapy with highest ranking of evidence. [5, 23, 39]
- **Limitations**: Many studies were small, lacked a blinded comparison (often were compared to wait-lists), and did not declare intention-to-treat analysis.
- **Evidence Gaps**: Additional CER studies are needed to consider:
    - Differences in long-term effects among psychological therapies
    - Key subgroups to better understand how patient characteristics and subtypes of BN alter effectiveness of treatment

Medication

- While pharmacological treatments have been shown to be acceptable and effective in treating BN, most of the studies are focused on adults. The efficacy of fluoxetine has been demonstrated by its ability to decrease binge/purge frequency in several placebo-controlled RCTs among adults.[29, 36].[37] Fluoxetine is FDA-approved for BN. Only one small trial of fluoxetine (n=10) has been conducted among adolescents.[43] It demonstrated a significant reduction in binging and purging symptoms. The

Combination therapy that includes medication and psychotherapy have been shown to be more effective than either treatment alone. [37]

- **Limitations**: Few studies were conducted among adolescents and have captured long-term follow-up.
- **Evidence Gaps**: Additional CER in adolescents with BN to determine the optimal dose and type of pharmacological intervention may be warranted.

Delivery of Services

- Unlike with AN, the stepped care approach has been empirically proven to be effective at tailoring the intensity of treatment necessary for different levels of BN severity (Hay et al, 2005). Stepped care, that starts with guided self-help and then refers non-responders to more intensive treatment (either medication or CBT or both), was found to be just as effective as immediate CBT/fluoxetine at reducing the frequency of binge eating and compensatory episodes in young people who have BN.[47]. While the step-care model shows promise, questions remain regarding when and how to transition from less to more intensive treatment and additional evidence is needed to demonstrate appropriateness among adolescents.
- **Limitations**: Studies did not test different sequences as part of stepped approach, had small sample size, and often excluded individuals with co-morbidities.
- **Evidence Gaps**: Additional CER may be warranted to evaluate:
    - Components of and sequences of stepped care that have the greatest impact on outcomes
    - Stepped care relative to outpatient care to determine the optimal intensity with which outpatient care should be delivered.

Ongoing Research

ClinicalTrials.gov results

We searched ClinicalTrials.gov on October 4, 2017. A total of 164 studies concerning "bulimia nervosa" were found. 151 studies were not relevant because they included inpatient treatments. Thirteen studies were relevant but also looked at another eating disorder condition. Two concerned solely patients with BN.

Of the 13 studies: 6 were randomized trials, 3 were single assignments, 2 were parallel assignments, one was an observational case only and one had not information on study design. One study was of an Internet-delivered cognitive behavioral therapy (CBT) for eight weeks while the other was an observation estimating the prevalence of attention deficit hyperactivity disorder (ADHD), and other neuropsychiatric disorders in patients with BN.

We performed a second new search for bulimia nervosa narrowing the search term to "adolescents" and only studies that were recruiting, not yet recruiting, active, not recruiting, enrolling by invitation. We identified 6 ongoing studies, 4 of which were removed because the

study sample included binge eating or overweight patients only. The remaining two were adolescent-specific observational studies.

Details of these trials can be found in Appendices 2 and 4.

Conclusion

While few large, high-quality studies have been conducted among adolescents, the strongest evidence to date for outpatient interventions is on psychological therapies, FBT for AN and CBT for BN. While the efficacy data for antidepressants and antipsychotics is limited for AN, some medications have been shown to be effective in adults with BN. Additional CER in adolescents with BN to determine the optimal dose and type of pharmacological intervention may be warranted. Multidisciplinary outpatient treatment is the preferred approach for medically stable individuals, however, additional questions remain about which components and/or combinations are necessary and sufficient at various stages of illness as well as which providers could best deliver the services. Additional CER investigating aspects and sequencing of stepped care, particularly for individuals with BN, as well as optimal intensity of outpatient care for both AN and BN is warranted.

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Appendix 1. Relevant Clinical Trials from ClinicalTrials.gov for AN

Condition	NCT ID	Study Design	Status	Intervention (Follow-up Length)	Eligibility	Enrollment	Study Start/End Date	Sponsor/Location
AN	NCT01933243	Randomized: Parallel Assignment	Recruiting	Fish oil (4 capsules daily) compared to placebo for 12 weeks	Ages 12-21 years	40	9/2016-2/2016	Nationwide Children's Hospital
AN	NCT02962726	Prospective: Case Control	Recruiting	Evaluate the effect of starvation and recovery in adolescent anorexia nervosa patients in regard to microbiome activity and composition and to elucidate potential connections between weight gain, depression and other comorbidities,	Ages 12-18 Years	200	11/2016-8/2019	RWTH Aachen University, Germany
AN	NCT03097874	Randomized: Parallel Assignment	Recruiting	Family Based Treatment (FBT) to adaptive FBT with an Intensive Parental Coaching (IPC) component. Follow-up at 3, 6 and 12-month	Ages 12-18 years	150	3/2017-2/2022	Stanford University, California, San Francisco
AN	NCT03288649	Prospective	Recruiting	Explore, within a qualitative approach, how a therapeutic alliance is established in three different clinical situations according to the adolescents, their parents and their physicians by crossing their perspectives.	Ages 12 to 18 years	180	1/2016-12/2017	Centre Hospitalier Victor Dupouy, France

AN	NCT02526927	Non RCT Single Group Assignment	Recruiting	HR-pQCT and DEXA for measure bone quality and quantity Blood samples, HR-pQCT and DEXA for measure bone quality and quantity	Ages 20 - 30 years & 10 - 20 years	50	5/2015-12/2017	Centre Hospitalier Universitaire de Saint Etienne, France
AN	NCT01057329	Case-Only: Prospective	Recruiting	Effectiveness of antipsychotics (olanzapine and aripiprazole), antidepressants (Duloxetine, Atomoxetine) by means of "Therapeutic Drug Monitoring" (TDM) in order to optimize dosage - effect relations and minimize unwanted side effects.	Ages 10-19 years	200	1/2010-2/2018	Medical University of Vienna
AN	NCT02400541	Randomized: Parallel Assignment (Phase 1)	Recruiting	Cognitive remediation therapy (10 biweekly sessions) compared to relaxation therapy	Ages 8 to 16 years	60	3/2015-3/2018	Assistance Publique - Hôpitaux de Paris, France
AN	NCT01301183	Randomized: Parallel Assignment (Phase 3)	Recruiting	Recombinant human (rh) insulin like growth factor-1 (rhIGF-1) with estrogen (to mimic pubertal levels of these hormones) versus administration of estrogen alone on bone metabolism	Ages 14-22 years	136	2/2011-12/2018	Massachusetts General Hospital
AN	NCT02795455	Randomized: Parallel Assignment	Recruiting	Interoceptive Exposure (IE) versus Family Based Therapy-Weight Gain Control (FBT-WG)	Ages 12-18 years	90	11/2016-6/2020	Icahn School of Medicine at Mount Sinai

AN	NCT02948452	Prospective Case Control	Recruiting	Responsiveness to reward in adolescents with restricting-type anorexia nervosa compared with non-clinical controls (fMRI)	Ages 13-19 Years	96	11/2015-11/2018	University of California, Los Angeles
AN	NCT02217384	Perspective: Cross-Sectional	Ongoing, but not recruiting	Investigate whether gut microbiota is altered in patients with AN	15 years or older	151	9/2014-9/2016	Odense University Hospital, Copenhagen
AN	NCT02980120	Case Control Prospective	Recruiting	Whether, on the basis of personality traits and personality disorders as well as specific cerebral activation patterns, differentiations can be identified among adolescent female patients with AN and BN in comparison to a healthy control group using multiple scales and measures	Ages 14-18 years	110	1/2015-11/2017	Medical University Innsbruck
AN	NCT00815815	Open Label RCT	Completed with results	Inpatient treatment for anorexia nervosa versus a sequenced treatment that transitions from higher intensity inpatient care to lower intensity outpatient care	16 Years and older	41	02/2004 – 02/2008	New York State Psychiatric Institute
AN	NCT00692185	Parallel Assignment RCT	Completed with results	2.5 mg, 5.0 mg, or 10.0 mg of olanzapine once each evening for 8 weeks vs. placebo.	16 Years and older	18	06/2008-08/2009	New York State Psychiatric Institute
AN	NCT00685334	(Open Label) Parallel Assignment RCT	Completed with results	olanzapine daily for 12 weeks vs. aripiprazole daily for 12 weeks.	16 Years and older (Child,	22	11/2003-09/2006	New York State Psychiatric Institute National

					Adult, Senior)			Institute of Mental Health (NIMH)
AN	NCT01190423	(Open Label) Single Group Assignment	Completed	Family Based Treatment Intervention vs Out-Patient Psychotherapy Treatment	Adult: 18 Years to 30 Years	30	07/2010-04/2016	Temple University National Institute of Mental Health (NIMH)
AN	NCT01740752	Single-blind RCT	Recruiting	Uniting Couples in the Treatment of Anorexia Nervosa (UCAN2) + CBT vs. CBT for a total of 44 sessions (1 year)	Adults	100	07/2012 – 03/2018	UNC/NIMH
AN	NCT01170117	Double-blind RCT	Ongoing	Olanzapine 2.5mg vs. placebo for 16 weeks (8 weeks) Results available	Adults	152	08/2010 – 06/2017	NIMH

Appendix 2. Relevant Clinical Trials from ClinicalTrials.gov for BN

Condition	NCT ID	Study Design	Status	Intervention (Follow-up Length)	Eligibility	Enrollment	Study Start/End Date	Sponsor/Location
BN	NCT02980120	Observational: Case Control	Currently recruiting participants	Whether, on the basis of personality traits and personality disorders as well as specific cerebral activation patterns, differentiations can be identified among adolescent female patients with AN and BN in comparison to a healthy control group using multiple scales and measures	Ages 14 - 18	110	12/2016-11/2017	Medical University Innsbruck, Austria
BN	NCT00345943	Perspective: Case-Control	Ongoing, but not recruiting participants.	Behavioral: Neuropsychological Testing: MRI	Ages 12-17	71	06/2009-1/2018	New York State Psychiatric Institute
BN	NCT02700620	Open-label RCT	Ongoing	Internet-delivered CBT for 8 weeks (none)	Adults	92	01/2016 – 12/2017	Sweden
BN	NCT00916071	Observational: Case only	Completed	Estimate the prevalence of ADHD, and other neuropsychiatric disorders, in outpatients with history of an eating disorder diagnosis	Adults: 18-55 years of age	64	08/2008 - 02/2010	Massachusetts

Appendix 3. Relevant Clinical Trials from ClinicalTrials.gov for AN, BN, and BED

Condition	NCT ID	Study Design	Status	Intervention (Follow-up Length)	Eligibility	Enrollment	Study Start/End Date	Sponsor/Location
BN, BED	NCT00768677		Completed	Topiramate (no additional information)	Child, Adult: 12-23 years		07/2003 – 10/2008	New York
AN,BN,	NCT02937259	Single Group assignment, open label	Enrolling by invitation only	Patient self-admission to inpatient treatment for 7 days	Adults: 18 & older	40	08/2014-12/2020	Stockholm, Sweden
AN, BN	NCT01990755	Open Label Parallel Assignment	Completed	CBT vs. Individual psychology brief psychotherapy (IBPP) vs CBT + OLANZAPINE (5 MG). each arm also has nutritional rehabilitation and delorazepam	Females: 15- 35 Years (Child, Adult)	112	05/2010-05/2013	University of Turin, Italy
AN, BN, PD	NCT00184301	Parallel Assignment RCT	Completed	Behavioral: inpatient treatment vs. intensive outpatient treatment consisting of two-weekly group sessions for 1 year	Females: 18 Years to 45 Years	43	09/2005 – 12/2011	Norwegian University of Science and Technology
AN, BED	NCT02382497	Double-blind RCT	Recruiting	Active vs. sham transcranial direct-current stimulation (tDCS) for 6 weeks (1 year)	Children age 13-18 years	160	07/2014 – 06/2017	Italy
AN, BN	NCT02702167	Double-blind RCT	Recruiting	High- vs. low-frequency repetitive transcranial magnetic stimulation (rTMS) for 15 days (12 weeks)	Adults	240	03/2016 – 03/2018	Canada
BN, BED	NCT02553824	Phase 1 open-label crossover	Recruiting	Phentermine/topiramate vs. placebo for 2 weeks (8 months)	Adults	30	07/2015 – 06/2018	Stanford
BN, BED	NCT02079935	Open-label, single-arm	Recruiting	CBT vs. physical activity and dietary therapy (FAKT) for 16 weeks (2 years)	Females 18-40 years	128	03/2014 – 06/2019	Norway

BN, BED	NCT02555553	Phase 2, open-label RCT	Recruiting	CBT-GSH with Noom Monitor vs. TAU for 12 weeks (1 year)	Adults 18-50 years	200	04/2016 – 01/2018	Icahn SOM/Kaiser Permanente
BN, BED	NCT02043496	Single-blind, single-arm	Recruiting	Integrative Cognitive-Affective Therapy (ICAT) vs. GSH-CBT for 16 weeks (6 months)	Adults	112	12/2013 – 08/2017	U of Minnesota
BN, BED	NCT02978742	Open-label RCT	Not yet recruiting	Standard meal monitoring and social support mobile app vs. additional coach feedback for 8 weeks (3 month)	Adults	300	09/2017 – 09/2019	Nova Scotia Health Authority
BN, BED	NCT02464345	Phase 2/3 single-blind RCT	Recruiting	Behavioral weight loss therapy integrated with CBT (Healthy Approach to weight management and Food in Eating Disorders, HAPIFED) vs. CBT-E for 6 months (1 year)	Adults	100	07/2015 – 12/2018	Brazil/Australia
BN, BED	NCT01832792	Single-blind RCT	Ongoing	Face-to-face vs. email self-help vs. waitlist for 12 weeks (6 months)	Adults ≥17 years	102	08/2013 – 08/2017	Oxford NHS

Table 1: Guidelines for the treatment of Anorexia Nervosa

Guideline	Recommendation for Setting	Recommendation for Nutritional Rehabilitation	Recommendation for Psychological Interventions	Recommendation for Pharmacological Interventions
APA	For underweight individuals with anorexia nervosa, the guideline recommends that hospital-based programs for nutritional rehabilitation should be considered	For patients who refuse to eat and require life-preserving nutrition, the guideline recommends nasogastric feeding.	The practice guideline strongly recommends family treatment for children and adolescents with eating disorders. For underweight individuals with anorexia nervosa, the guideline recommends that hospital-based programs for nutritional rehabilitation should be considered	Although psychotropic medications should not be used as the sole or primary treatment for anorexia nervosa, they have been used as an adjunct treatment when nutritional rehabilitation programs alone are ineffective in restoring patients' normal weight or when patients demonstrate significant comorbid psychopathology such as disabling obsessive-compulsive, depressive, or anxiety symptoms. However, because anorexia nervosa symptoms and associated features such as depression may remit with weight gain, decisions concerning the use of medications should be deferred if possible until patients' weight has been restored.

NICE	Admit people with an eating disorder whose physical health is severely compromised to a medical inpatient or day patient service for medical stabilisation and to initiate refeeding, if these cannot be done in an outpatient setting. Do not use an absolute weight or BMI threshold when deciding whether to admit people with an eating disorder to day patient or inpatient care. When reviewing the need for inpatient care as part of an integrated treatment programme for a person with an eating disorder: 1)do not use inpatient care solely to provide psychological treatment for eating disorders 2)do not discharge people solely because they have reached a healthy weight.	Only offer dietary counselling as part of a multidisciplinary approach.	Consider anorexia-nervosa-focused family therapy for children and young people (FT-AN), delivered as single-family therapy or a combination of single- and multi-family therapy If FT-AN is unacceptable, contraindicated or ineffective for children or young people with anorexia nervosa, consider individual CBT-ED or adolescent-focused psychotherapy for anorexia nervosa (AFP-AN).	Do not offer medication as the sole treatment for anorexia nervosa.

	For people with anorexia who are not having treatment and who do not have severe or complex problems: discharge them to primary care and tell them they can ask their GP to refer them again for treatment at any time			
AACAP	Psychiatric hospitalization, day programs, partial hospitalization programs, and residential programs for eating disorders in children and adolescents should be considered only after outpatient interventions have been unsuccessful Treatment of eating disorders in youth usually involves a multi-disciplinary team that is developmentally aware, sensitive, and skilled in the care of children and adolescents with eating disorders (CS***).***	The dietician may be a consultant to the pediatrician or therapist about any nutritional concerns. Some dieticians may provide direct consultation to families and patients, depending on the overall treatment approach being utilized. Studies do not support the use of nutritional counseling as a sole treatment for eating disorders	Outpatient psychosocial interventions are the initial treatment of choice for children and adolescents with eating disorders.	The use of medications, including complementary and alternative medications, should be reserved for comorbid conditions and refractory cases

Table 2: Guidelines for the Treatment of Bulimia Nervosa

Guideline	Recommendation for Setting	Recommendation for Nutritional Rehabilitation	Recommendation for Psychological Interventions	Recommendation for Pharmacological Interventions
APA	Outpatients treatment is recommended except when there are complicating factors (serious medical, suicide) or patient doesn't respond to outpatient treatment.	The guideline recommends a normalization of nutrition and eating habits as a central goal in treatment of people with bulimia.	CBT is the most effective and best-studied intervention for BN in adults IPT is recommended for patients who do not respond to CBT. Self-help approaches that used highly structured CBT were also found to be promising. Family Based Therapy (FBT) should be considered whenever possible especially when dealing with adolescent patients.	Tricyclic antidepressants, particularly the selective serotonin reuptake inhibitors. With moderate confidence, the guidelines recommend the combination of antidepressant medication with CBT.
NICE	Outpatient is recommended	Work with nutritionist if needed	Bulimia nervosa focused family therapy should be offered. Bulimia nervosa focused guided self-help programs should: • use CBT self-help materials • supplement the self-help program with brief supportive sessions (4-6 lasting 20 mins each over 16 weeks)	Medication should not be offered as the sole treatment

			if self-guided help is ineffective after 4 weeks of treatment, individual focused CBT should be considered	
AACAP	Outpatient psychosocial interventions are the initial treatment of choice. Psychiatric hospitalizations, day programs, partial hospitalization programs, ad residential programs for eating disorders should be considered only after outpatient interventions have been unsuccessful.	Recommends a team of practitioners to include a dietician. Does not recommend nutritional counseling as a sole treatment.	FBT recommended for most cases of short duration BN in young patients Adolescent version of CBT may be appropriate. Interpersonal Psychotherapy should be used for cases of BN as an alternative to CBT	Recommend use of antidepressants for comorbid disorders and refractory case; Use antidepressant as a second line of treatment for adolescent BN.