Innovations in Treating Co-Morid Mental Illness in Eating Disorders
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DISCLOSURES

- Consultant
  - EDCare
  - Doximity
- Research support
  - Compass Pathways (psilocybin trial)
- Ownership
  - Next Generation Therapies

OVERVIEW
IMPORTANT TOPICS BUT LITTLE DATA

- Types of Eating Disorders (ED)
- Prevalence of co-morbid disorders
- Confounds
  - Few controlled trials of ED treatments
  - Few studies of co-morbid disorder response
  - Limited research – Mainly rely on suggestions from non-controlled trials

Subtype	Lifetime Prevalence	DSM5 DESCRIPTION
Anorexia Nervosa	0.6%	Restriction of energy intake leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Intense fear of gaining weight, even though underweight. Body image disturbance, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight
Bulimia Nervosa	1.0%	Recurring binge eating episodes: Eating large amounts of food within a 2-hour period and sense of lack of control. Recurring inappropriate compensatory behavior (vomiting, laxatives, exercise, diet pills) Binge eating and compensatory behaviors occur, on average, at least once a week for three months Self-evaluation is unduly influenced by body shape and weight
Binge-Eating Disorder	2.8%	Recurring episodes of eating large amounts of food, more than most people would eat in similar circumstances in a short period of time. Eating rapidly, eating beyond fullness and secret eating marked with distress around binges. Sense of lack of control over eating during the episode. Binge episodes average at least once a week for three months
ARFID	0.3-15.5%	Eating or feeding disturbance so pervasive that the person is unable to meet appropriate nutritional needs, resulting in: significant weight loss, nutritional deficiency, dependency on nutritional supplements, or interference in social functioning. Not explained by a lack of food being available, and not related to what the person believes about his/her size, weight, and/or shape. This disturbance is not caused by a medical condition or another mental disorder

Lifetime Co-morbidity of ED with other Core Disorders (DSM-IV) in US Adults National Comorbidity Survey Replication (NCS-R)

Hudson et al Biol Psychiatry 2007; Sanchez-Cerezo 2023

	Anorexia Nervosa (%)	Bulimia Nervosa (%)	Binge-Eating Disorder (%)
Any Anxiety Disorder	48	81	65
Any Mood Disorder	42	71	46
Any Impulse Disorder	31	64	43
Any Substance Use Disorder	27	37	23
Any DSM-IV Mental Disorder	56	95	79

ARFID: Anxiety Disorders 9 to 72%; Autism Spectrum (8 to 55%)

Other confounds and comorbidity

- Treatment resistance (Halmi 2013)
  - 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.
  - 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.
- Personality and Temperament (Sansone and Sansone 2011)
  - In contrast to reported rates in the general population of eight percent, obsessive compulsive personality is present in approximately 22 percent of individuals with anorexia, restricting type.
  - In contrast to rates in the general population of six percent, borderline personality is present in approximately 25 percent of individuals with anorexia nervosa, binge-eating purging type, and in 28 percent of individuals with bulimia nervosa.

ED symptom severity and Psychiatric Comorbidity

Spindler and Milos 2007

- Affective and anxiety-related disorders linked with increased intensity of weight and appearance-related fears and concerns
  - Binge and purge frequency associated with anxiety disorders, substance use disorders, and cluster B personality disorders
  - Dieting frequency related to anxiety disorders
  - Axis I anxiety disorders more closely related to ED symptom severity than affective or substance use disorders

ANOREXIA NERVOSA

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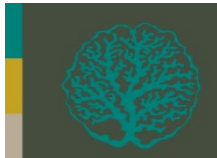

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Anorexia Nervosa: Puzzling Symptoms Serious and Severe Disorder

Kaye and Bulik JAMA Psychiatry 2020

- Body image distortions, fear of being fat
  - No satisfactory loss of weight
- Severe restricted eating, emaciation
  - But preoccupation with food
- Denial of illness, lack motivation for treatment
- Excellent student
  - But limited ability to learn to change
- Course (Kiely 2024; Steinhausen 2002)
  - 20 to 30+% chronically ill (Severe and Enduring AN)
  - 5%-10%+ die – starvation, suicide,
  - Longitudinal study over 22 years (Eddy 2017)
    - » Eventually Recovered
      - 63% with AN
      - 68% with BN

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Anorexia Nervosa

- AN has the highest mortality rate of any psychiatric disorder
  - For females 15-24 years old with AN, mortality rate is 12x higher than death rate of all causes of death. 5.1 deaths per 1000 people with AN per year (Kaye and Bulik 2020)
- Lifetime suicide attempts range from 3 to 29.7%. (Pisetsky 2015)
- Frequent medical consequences

Terminal AN Gaudiani 2022
Advocating Medically Assisted Suicide

- Severe and Enduring AN :
  - "Treatment seems both futile and harmful."
  - "No level of harm reduction provides achievable or adequately ameliorates their suffering"
  - Presented case series
    - All 3 cases had OCD
    - 2 of 3 cases mention substantial anxiety

New Perspective for ED: Genetics and ED

- ED often occur in families (Lilienfeld 1998; Strober 2000; Bulik 2021)
  - AN and BN cross transmitted in families – shared vulnerability?
  - Increased family risk:
    - full or partial AN syndromes, ED NOS
    - mood disorders, OCD and OCPD
- Twin studies:
  - AN Approximately heritable risk 28 to 74% (Bulik 2021)
- ED have significant genetic correlations with other psychiatric disorders (Watson 2019; Smeland 2023)
  - Genetic associations with OCD, Major depression, Schizophrenia, anxiety, Neuroticism, and Parkinson's Disease
- **Suggests powerful neurobiology is genetically transmitted**
- **History of Medicine: Understanding disease mechanisms accelerates development of effective treatments**

Anxiety

Lilenfeld 1998, Dellava 2010, Raney 2008, Bloss 2011, Steinglass 2014

- **Most AN and half relatives have anxiety disorder**
- **Anxiety premorbid, persistent, associate with restrictive eating**
- **Anxiety associated with poor outcome**
  - **Lower BMI and greater caloric restriction**
  - **Greater ED psychopathology**
  - **Poor outcome**
  - **Non responsive to benzodiazapines**
  - **GABA gene alterations**

ED and Anxiety, Fear Growing Interest

Strong signal, replicated data

Physiology & Behavior 152 (2015) 466–472

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

Anorexia nervosa as a motivated behavior: Relevance of anxiety, stress, fear and learning

Angela S. Guarda *, Colleen C. Schreyer, Gretha J. Boersma, Kellie L. Tamashiro, Timothy H. Moran

Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, USA

Neuroscience and Biobehavioral Reviews 95 (2018) 383–395

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Fear as a translational mechanism in the psychopathology of anorexia nervosa

Stuart B. Murray[a,*], Michael Strober[b], Michelle G. Craske[c], Scott Griffiths[e], Cheri A. Levinson[d], Irina A. Strigo[a,f]

Neuropsychopharmacology (2011) 36, 2222–2232

www.neuropsychopharmacology.org

Genetic Association of Recovery from Eating Disorders: The Role of GABA Receptor SNPs

Cinnamon S Bloss[1], Wade Berrettini[2], Andrew W Bergen[3], Pierre Magistretti[4], Vikas Duvvuri[5], Michael Strober[6], Harry Brandt[7], Steve Crawford[7], Scott Crow[8], Manfred M Fichter[9], Katherine A Halmi[10], Craig Johnson[11], Allan S Kaplan[12,13,14], Pamela Keel[15], Kelly L Klump[16], James Mitchell[17,18], Janet Treasure[19], D Blake Woodside[13,14], Enrica Marzola[1,20], Nicholas J Schork[1,21] and Walter H Kaye*,[5]

RESEARCH ARTICLE

Anxiety in Anorexia Nervosa and its Management Using Family-Based Treatment

Tom Hildebrandt[1]*, Terri Bacow[1], Mariana Markella[1] & Katharine L. Loeb[1,2]

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[2]School of Psychology, Fairleigh Dickinson University, Teaneck, NJ, USA

Associations between mealtime anxiety and food intake in anorexia nervosa

E. Caitlin Lloyd[1,2], Chanel Powell[1,2], Janet Schebendach[1,2], B. Timothy Walsh[1,2], Jonathan Posner[1,2], Joanna E. Steinglass[1,2]

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High Anxiety and Harm Avoidance

Exacerbated by state of illness or history of a lifetime Axis I anxiety disorder

Category	Ill ED	Ill ED	Rec ED	Rec ED	Control
Lifetime Anxiety Disorder	yes	no	yes	no	no
State anxiety	50 ± 14*	42 ± 13*	41 ± 12*	35 ± 10*	27 ± 6
Trait anxiety	54 ± 13*	46 ± 13*	45 ± 12*	39 ± 10*	29 ± 7
Harm avoidance	22 ± 7*	17 ± 7*	19 ± 7*	14 ± 6*	11 ± 5

Price Foundation Collaboration. Kaye et al, *Am J Psychiatry*. 2004; 161:2215–2221
Comparison of 672 AN and BN women vs. 694 healthy control women

***All ED groups significantly elevated (p<.0001) compared to controls**

Spielberger State and Trait Anxiety Inventory;
Harm Avoidance from Cloninger Temperament and Character Inventory a measure of anxiety, inhibition, inflexibility

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Anxiety Disorders (AD)
Lifetime and Premorbid Rates

Study	ED	n	Lifetime AD	AD before ED
Deep 95	AN	24	68%	58%
Bulik 97	AN	68	60%	54%
Bulik 97	BN	116	57%	54%
Godart 00	AN	29	83%	62%
Godart 00	BN	34	71%	62%
Kaye 04	AN,BN	672	64%	61% 23% OCD 13% Social Phobia

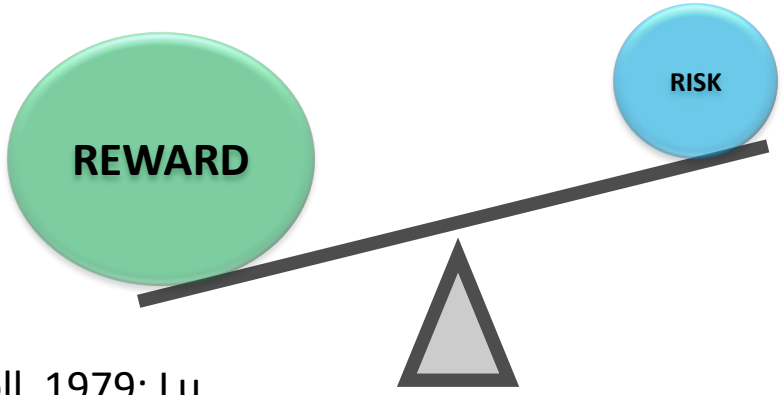
GENETICS: Diagnosed Anxiety Disorders and the Risk of Subsequent AN: Danish Population Register

Meire, Bulik, Thornton, Mattheisen, Mortensen, Petersen EEDR 2015

- Determined the risk of anorexia nervosa in patients admitted to inpatient or outpatient services with severe anxiety disorders compared with those in the general population
  - OCD, social phobia and GAD in childhood significantly increased the risk of anorexia nervosa in adolescents
- Cross-generational analyses, examined the effect of parental anxiety disorder diagnoses on offspring risk for anorexia nervosa
  - paternal diagnosis of panic disorder increased the offspring's risk of anorexia nervosa.
- "Anxiety disorders and anorexia nervosa share etiological mechanisms and/or anxiety represents one developmental pathway to anorexia nervosa"
- Twin studies:
  - Shared genetic susceptibility of AN and anxiety disorders (Keel 2005)
  - Unaffected co-twin of patients with ED likely to have an anxiety disorder (Keel 2005)
  - Comorbidity between AN and panic disorder (Walters & Kendler 1995)

Fasting and Hunger Modifies Behavior in people and animals

- Hunger increases motivational aspects of food, money, etc..
  (Goldstone 2009; Kringelbach 2003, Tataranni 1999, Uher 2006; Tataranni 1999; Haase 2009)
  - **Activates regions associated with reward and motivation**
  - Reduces top down inhibitory self-control.
- When hungry
  - Healthy humans are less risk-averse (Symmonds 2010; Levy 2013)
  - Enhances sensitivity to drugs of abuse in animals (Carr, 2002; Carroll, 1979; Lu, 2003; Shalev, 2001)
  - If shopping can lead to purchases of unhealthy, higher-calorie foods (Tal 2013)



- **Why most people struggle to lose a few pounds**
- **Do AN have abnormal response to hunger ?**

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What is Different About Eating Behaviors in AN?

- Healthy people: Singh 2014
  - Irritable, tense when hungry;
  - Pleasure/reward when eating
- Anorexia nervosa: Kaye 2003; Strober 1995; Vitousek 1994; Steinglass 2010, Marzola 2013, Khalsa 2018
  - Food associated with anxiety, uncomfortable feelings
  - Anxiety reducing character to dietary restraint (or even reward?)
- Is there a primary disturbance of eating behavior

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NEUROBIOLOGY OF ANXIETY

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Relation of GABA Gene in AN to anxiety, outcome

Bloss 2011 Neuropsychopharmacology Price Foundation Study

- GABA is major inhibitory neurotransmitter in the brain and modulate anxiety states
- Tested 5151 single-nucleotide polymorphisms (SNPs) in approximately 350 candidate genes for association with recovery from ED in 1878 women. Compared 361 ill ED to 115 recovered ED.
- An intronic SNP (rs17536211) in GABRG1 subunit was associated with trait anxiety and poor outcome in ED
  - This subunit may reduce sensitivity to benzodiazepines
  - Controlled trial (17 AN) alprazolam had no effect on caloric intake or anxiety (Steinglass et al 2014)

Serotonin (5-HT) AND ANOREXIA NERVOSA

- Increase CSF 5-HIAA (brain serotonin) after recovery from AN (Kaye 1991)
- Altered Brain 5-HT systems contribute to ED (Brewerton 1995)
- Modulation of appetite {Blundell, 1984;Leibowitz, 1998;Wurtman, 1979}.
  - Increased intrasynaptic 5-HT tends to reduce food consumption.
- Increased brain 5-HT could contribute to anxious, harm-avoidant, obsessional symptoms {Charney, 1990;Cloninger, 1987;Soubrie, 1986}.
  - Harm Avoidance thought to reflect serotonin metabolism (Cloninger 1988, 1986, 1993)
  - AN tend to be anxious, obsessional, perfectionistic, and harm avoidant.
    - Such traits are premorbid and persist after recovery {Bulik, 1995;Deep, 1995;Kaye, 1992;Srinivasagam, 1995;Strober, 1980}
    - Suggests that such behaviors are not just secondary to malnutrition.

NO FDA APPROVED MEDICATIONS FOR AN

SEE THESE COMPREHENSIVE OVERVIEW MEDICATION IN ED

- Frank GKW. Pharmacotherapeutic strategies for the treatment of anorexia nervosa - too much for one drug? Expert Opin Pharmacother. 2020 Jun;21(9):1045-1058. doi: 10.1080/14656566.2020.1748600. Epub 2020 Apr 13. PMID: 32281881; PMCID: PMC7491209.
- Mitchell JE, Roerig J, Steffen K. Biological therapies for eating disorders. Int J Eat Disord. 2013 Jul;46(5):470-7. doi: 10.1002/eat.22104. PMID: 23658094; PMCID: PMC4372845.

MEDICATION and ED

- FDA approved Medication
  - Fluoxetine (Prozac) for bulimia nervosa
  - Lisdexamfetamine (Vyvanse) for BED
  - None for anorexia nervosa, ARFID
- Few RCT
- Little data on comparisons of medications
- Trials tend to be short term - Little data on long-term, durability, relapse with discontinue, or comorbid disorders

Anorexia Nervosa – APA Guidelines 2023

- Adolescents and emerging adults:
  - Family Based Treatment (FBT)
- Adults: ED focused psychotherapy, goals:
  - Normalize eating, weight
  - Addressing psychological aspects (fear of weight gain, body image disturbances)

RESOURCES

- NICE guideline (National Institute (UK) for Care and Health Excellence)
  - Published: 23 May 2017
  - Last updated: 16 December 2020
  - www.nice.org.uk/guidance/ng69
- Practice guideline for the treatment of patients with eating disorders (revision). American Psychiatric Association Work Group on Eating Disorders. Am J Psychiatry. 2000 Jan;157(1 Suppl):1-39. PMID: 10642782.

National Institute of Health and Care Excellence (NICE) Guidelines

Wittek 2021, Steinhausen2002, Eddy 2017, Fichter 2017

- AN treatment needs to be multidisciplinary including medical care and weight monitoring as well as psychological interventions.
- Only half of all patients receive AN treatment achieve full recovery after 4 to 10 years.
- Longitudinal studies showed that after 20 years of suffering from AN, recovery rates are still very low, ranging from 40 to 63% .

Randomized controlled trial of three psychological treatments for anorexia nervosa

Bryne et al 2017

- Compared three psychological treatments for AN:
  - Specialist Supportive Clinical Management,
  - Maudsley Model Anorexia Nervosa Treatment for Adults
  - Enhanced Cognitive Behavioral Therapy
- Multi-center randomized controlled trial with outcomes assessed at pre-, mid- and post-treatment, and 6- and 12-month follow-up by researchers blind to treatment allocation.
- 120 individuals with AN were recruited from outpatient treatment settings in three Australian cities and offered 25–40 sessions over a 10-month period. Primary outcomes were body mass index (BMI) and eating disorder psychopathology. Secondary outcomes included depression, anxiety, stress and psychosocial impairment
- Treatment was completed by 60% of participants and 52.5% of the total sample completed 12-month follow-up. Completion rates did not differ between treatments.
- No significant differences between treatments on continuous outcomes; all resulted in clinically significant improvements in BMI, eating disorder psychopathology, general psychopathology and psychosocial impairment that were maintained over follow-up.
- There were no significant differences between treatments with regard to the achievement of a healthy weight (mean = 50%) or remission (mean = 28.3%) at 12-month follow-up.
- **The findings add to the evidence base for these three psychological treatments for adults with AN, but the results underscore the need for continued efforts to improve outpatient treatments for this disorder.**

Maudsley (Family Based Treatment (FBT)) for Youth with Anorexia Nervosa

- Russell, Eisler, Lock, LeGrange
- Agnostic view of cause of illness (Non blame)
- Family made responsible to re-feed child (Empowerment)
- Non authoritarian therapeutic stance (Joining)
- Separation of child and illness (Respect for adolescent)
- Highly focused, staged treatment
- Emphasis on behavioral recovery rather than insight and understanding
- Indirect approach to improving family functioning
- Supports gradually increased independence from therapy

Maudsley / FBT Adolescents with AN

Gorrell 2019, Lock & Le Grange, 2019

- First-line treatment of adolescents with AN
- Strengths
  - End-of-treatment remission rates are ~40%
- Limitations
  - More effective in Outpatient, less severely ill, younger AN
  - Some do not respond, difficult treatment for families
  - “Instinctive” parental input
  - Few deeply trained FBT therapists
  - Does not reverse temperament, personality

Medications AN

Few controlled trials in AN; Present evidence from uncontrolled trials

- SSRI
  - Ill AN:
    - SSRIs not effective for weight restoration when someone is in an emaciated state, {Ferguson, 1999}.
    - Fassino, 2002: Citalopram associated with improved anxiety, depression, impulsivity, and obsessive compulsive symptoms, BUT NOT shown to help with weight gain
    - No controlled trials of SSRIs have been done in ill AN
  - After Weight Restoration
    - Kaye (2001) fluoxetine restricting AN (AN-R): reduced relapse
    - Walsh (2005) fluoxetine AN-R and bulimic AN (AN-BP): No discernible benefit

Medications AN

Few controlled trials in AN; Present evidence from uncontrolled trials

- Atypical Antipsychotics
  - RCT Olanzapine (Attia 2019): Modest effect on weight gain Olanzapine > placebo, about 1 lb. more per month. No effect on obsessional thought or anxiety
  - RCT Quetiapine (Powers 2012): No difference weight gain or core symptoms
  - RCT Risperidone (Hagman 2011) No benefit for risperidone in adolescents during weight restoration
  - Aripiprazole (open trials)
    - Reduced distress around eating, and core ED symptoms (Trunko 2010 case reports)
    - Arip+SSRI > Olanzapine+SSRI or SSRI: reduction anxiety, depression, core ED symptoms (Marzola 2015 chart review)
    - Arip > TAU: greater weight gain (Frank 2016 chart review)
    - No placebo controlled trials of aripiprazole

BULIMIA NERVOSA

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Fluoxetine in the Treatment of Bulimia Nervosa

Fluoxetine BN Collaborative Group, Arch Gen Psychiatry 1992

- 8 week double blind study
- Fluoxetine 60mg and 20mg vs placebo
- 287 BN women as OP
- 60mg fluoxetine superior to placebo
  - Decrease frequency of weekly binge-eating and vomiting episodes
  - Improvement in depression, carbohydrate craving, pathologic eating attitudes and behaviors
  - Fluoxetine associated with insomnia, nausea, asthenia, tremor
- 20mg dose modest response

BINGE EATING DISORDER

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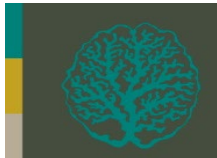

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Pharmacological Treatment of BED

Reas and Grillo 2015

- Conclusions and Recommendations
  - Jan 2015 FDA approved Lisdexamfetamine for moderate to severe BED (minimum of 3 or more days of binge-eating per week)
    - Not indicated for weight loss – similar meds have been associated with cardiovascular adverse events
    - DEA-controlled substance – warning – high potential abuse, dependency, need for monitoring for abuse
  - 2 anti-obesity meds (sibutramine, rimonabant) have been withdrawn due to safety concerns
- Most pharma research small scale RCT with mixed results with little to modest clinical benefits. Limited power
  - Majority BED research industry funded done in US, industry sponsored
- Studies tend to be of short duration (6 to 24 weeks) with few follow up- thus little guidance about optimum length of treatment, durability, risk of relapse after med discontinuation
- Tend to exclude subjects with psychiatric comorbidities, and limited racial/ethnic and gender diversity
- Majority do not achieve abstinence and little weight loss over short term

Pharmacological Treatment of BED

Reas and Grillo 2015

- SSRI (fluoxetine) vs placebo, other SSRI, or CBT
  - Mixed results: Binge eating, weight loss, comparison to placebo, CBT
- Antiepileptic (topiramate 3 RCT)
  - Only medication that resulted in substantial weight loss in BED
  - High rates of adverse events, and dropout)
- Anti-Obesity Medications
  - 3 RCT for Orlistat – 2 found enhanced weight loss but not reduced binge eating
- Stimulant Medication (Lisdexamfetamine) FDA approved
  - McElroy 2015 50mg and 70mg dose superior to placebo reduction binge eating and weight loss (not approved for weight loss by FDA – safety and efficacy for obesity not indicated or recommended for weight loss)

Caveats Treatments

- Binge disorders - Few patients are abstinent – good outcome base on reduction of frequency
- Little data on comparisons of medications
- SSRI doses sometimes have to be escalated to continue efficacy
- Trials tend to be short term - Little data on long-term, durability, relapse with discontinue, or comorbid disorders
- BN: Meds often adjunct to CBT (gold standard)

ARFID

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MIRTAZAPINE ASSOCIATED WITH SHORTER HOSPITAL STAYS FOR ARFID – RETROSPECTIVE CHART REVIEW

Chishti, Groh, Maginot, Adler, Shott, Kaye, Frank, IJED 2025

- A few case reports have been published

- Case reports suggested that mirtazapine could be beneficial for ARFID treatment (Naguy et al. 2023; Naviaux 2019; Gray 2018).
- Mirtazapine is a tetracyclic antidepressant which improves low appetite, decreases nausea and vomiting, and supports gastric emptying, typical associated symptoms of ARFID (Bhattacharjee et al. 2019; Iglesias-Escabi et al. 2022; Lalani et al. 2023).
- Mirtazapine is an antagonist at serotonin 2A, 2C, and 3, alpha-1 and 2A adrenergic, and histamine H1receptors, and is an agonist at kappa opioid receptors (Wishart et al. 2018). Mirtazapine leads to the release of norepinephrine and serotonin, neurotransmitters that affect mood and anxiety, while its kappa opioid receptor agonism has analgesic effects (Wishart et al. 2018; Anttila and Leinonen 2001). Mirtazapine is FDA-approved for adults with major depressive disorder. It is often used off-label for insomnia, anxiety, post-traumatic, stress, or obsessive-compulsive disorders due to its sedative, antiemetic, anxiolytic, and appetite-stimulant effects (Jilani et al. 2024).
- Hospital records from 87 children and adolescents with ARFID treated in an inpatient medical stabilization program were analyzed.
- Treatment outcome was tested for the effects of mirtazapine on weight gain, length of hospitalization, and duration of nasogastric feeding tube versus orally delivered nutrition.
- Other medications prescribed (selective serotonin reuptake inhibitors, dopamine D2 receptor partial agonist aripiprazole, and dopamine D2 receptor antagonists) and comorbid disorders (depression and anxiety) were included in the analysis.
- Results: Age was similar between individuals treated with or without mirtazapine (12.7 ± 1.0 years vs. 13.1 ± 1.0 years). Thirty-eight (44%) patients with ARFID were treated with mirtazapine. MANOVA indicated significant effects of mirtazapine and being associated with shorter hospital stays and a lower number of nasogastric feeding tube days Mirtazapine treatment was associated with a faster rate of weight gain

MIRTAZAPINE ASSOCIATED WITH SHORTER HOSPITAL STAYS FOR ARFID – RETROSPECTIVE CHART REVIEW

Chishti, Groh, Maginot, Adler, Shott, Kaye, Frank, IJED 2025

- A few case reports have been published
- Conclusion; In a highly controlled environment, all patients reached a comparable target weight,
- But patients treated with mirtazapine did so faster. Further research should investigate the clinical effects and underlying mechanisms of mirtazapine in patients with ARFID.
- Results: Age was similar between individuals treated with or without mirtazapine (12.7 ± 1.0 years vs. 13.1 ± 1.0 years). Thirty-eight (44%) patients with ARFID were treated with mirtazapine.
- Significant effects of mirtazapine for a lower number of nasogastric feeding tube days and a faster rate of weight gain
- In this highly controlled environment, all patients reached a comparable target weight, but patients treated with mirtazapine did so faster. Further research should investigate the clinical effects and underlying mechanisms of mirtazapine in patients with ARFID.
- Anecdotally, patients reported reduced anxiety and improved mood – but not known if this contributed to weight gain and eating.
- Gray 2018 average dose of mirtazapine was 25.5 mg (SD 17.9, range 7.5–60).

OCD and AN

Levinson 2019; Simpson 2013; Leonard and Bradley Riemann 2013

- OCD found in 35 to 44% of AN and AN is found in 10% of females with OCD
- AN-OCD associated with younger age of onset and poorer prognosis in AN
- AN and OCD (GWAS and twin studies) are genetically associated
- For OCD, evidence-based treatments include cognitive behavioral therapy (CBT) emphasizing exposure and response prevention (ERP), the use of serotonin reuptake inhibitors (SRI (clomipramine and selective SRIs), or a combination of these therapies. For eating disorders, evidence-based treatments include CBT emphasizing eating monitoring and cognitive restructuring (for both anorexia nervosa [AN] and bulimia nervosa [BN]), the use of fluoxetine (for BN), and weight restoration (for AN).
- Clinical experience: OCD – AN often not respond to SRI or may need higher doses

PTSD

Brewerton 2023; Schaefer 2022

- PTSD proposed to be a significant risk factor for the development of an eating disorder and co-occurs with eating disorders at a much higher rate than the general population. In community, 6.8% of adults and up to 8% of adolescents in the United States will meet the diagnostic criteria for PTSD at some point in their lives, studies have found that on average 25% of people with eating disorders experience co-occurring PTSD. Prevalence rates for PTSD are even higher among those with bulimia nervosa (BN), with studies showing up to 45% of subjects having both disorders.
- Research has also found that those with eating disorders and co-occurring PTSD experience more complex and severe eating disorder symptoms, are more likely to have binge-purge types of eating disorders (e.g., binge eating disorders (BED), bulimia nervosa (BN) etc.), drop out of treatment, have other co-occurring mental illnesses, increased risk of suicidality and poorer treatment outcomes than those without PTSD. For example, a study of hospital patients with BN and other specified food or eating disorders (OSFED) found that those with PTSD were over 2 times more likely to leave treatment early than those without PTSD.
- Recent work integrating empirically supported interventions for both eating disorders (enhanced cognitive behavior therapy [CBT]) and PTSD (cognitive processing therapy) among adults suggests that integrated CBT might be more effective at reducing PTSD symptoms than eating disorder treatment alone while producing similar outcomes for eating disorder symptoms
- MEDS: SSRI, atypical antipsychotics, topiramate

What About:

- Ketamine
- Psychedelics
- GLP1 agonists
- Cannabinoids
- TMS
- DBS

KETAMINE Response in ED

Ragnhildstveil et al 2022

Author year	Design	Sample, Mean Age	Diagnosis	Drug Administration	Outcome
Dechant 2020	Case study	N=1, 24	AN-R, MDD	IV	Partial remission, depression, suicide
Mills 1998	Case series	N=12, 33.3	AN-R, AN-BP	IV	Partial remission, depression and OCD related ED symptoms
Ragnhildstveil 2021	Case study	N=1, 21	BN-BP	IV	Complete, sustained, ED symptoms
Schwartz 2021	Case series	N=4, 36.8	AN-R, TRD EN-NOS, TRD	IV, IM	Partial remission, depression, anxiety, ED symptoms
Scolnick 2020	Case study	N=1 29	AN-R MDD	IV	Complete, sustained remission, depression and OCD ED symptoms

Results are encouraging, but limited to case series and reports

Utility for clinical nonresponders

Research needed to explore subgroup response, establish safety protocols, and optimize dosing.

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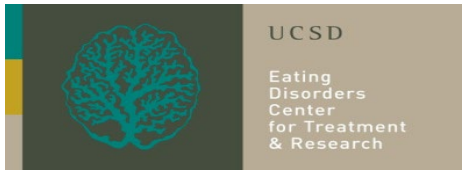

Psychedelic-assisted therapy

- Psilocybin (Knatz-Peck 2023) 10 patients with AN – open trial
  - Modest Group reduction anxiety and ED symptoms

Psychedelics (Calder 2023) Psychedelic-assisted therapy has recently shown potential in the treatment of several common comorbidities of eating disorders, including mood disorders, post-traumatic stress disorder, and substance use disorders.

This review summarize preliminary data on the efficacy of psychedelic-assisted therapy in people with anorexia nervosa, bulimia nervosa, and binge eating disorder, which include studies and case reports of psychedelic-assisted therapy with ketamine, MDMA, psilocybin, and ayahuasca. They found preliminary evidence that psychedelic-assisted therapy may be effective in the treatment of anorexia nervosa and bulimia nervosa, with very little data available on binge eating disorder. Regarding mechanisms, psychedelic-assisted therapy may be able to improve beliefs about body image, normalize reward processing, promote cognitive flexibility, and facilitate trauma processing.

rTMS in AN Literature review (Kim 2023)

- 33 articles (pilot, case series and case reports and 4 RCT)
- 16 studies included
  - DLPFC, DMPFC, insula
  - rTMS is safe and well tolerated in AN
  - Subset AN not respond well to TMS
    - Open label case series ED PTSD target DMPFC: low BMI had poor response compared to higher BMI
  - Recommend longer follow-up, large RCT compare sham vs real TMS

TMS in AN
Bahadori 2025

- Systematic review and meta-analysis examined the impact of TMS on patients with AN and evaluated any potential adverse effects.
- Search according to PRISMA guidelines and comprehensively analyzed data from multiple databases, including Pubmed, Scopus, Embase, Web of Science, and the Cochrane Library, up to September 13th. Statistical analysis utilized the Comprehensive Meta-analysis software version 3.0. Review encompassed 17 studies, with nine undergoing meta-analyses. The primary target for TMS was the dorsolateral prefrontal cortex, with two studies targeting the dorsomedial prefrontal cortex, one targeting the insula and one targeting the inferior parietal lobe.
- The findings revealed a significant increase in body mass index (BMI) following TMS (SMD: -0.025, 95% CI: -0.0505 to -0.005, P-value = 0.045). Additionally, the Eating Disorder Examination Questionnaire (EDE-Q) score was quantitatively reported in six studies, which permitted its inclusion in the meta-analysis. The analysis exhibited a significant decrease in EDE-Q score after TMS (SMD: 0.634, 95% CI: 0.349-0.919, P-value < 0.001). Subgroup analysis based on TMS session duration indicated that the effect size of TMS on EDE-Q score is more pronounced when the session duration exceeds 20 min.
- Best to review sham vs TMS
- Conclusion: TMS represents an effective therapy for patients with AN, leading to improvements in both BMI and core symptoms of AN, with minor and transient side effects.

TMS Real vs Sham

- Dalton 2018: Adult AN (SEAN) 20 sessions/4 weeks L DLPFC high frequency rTMS, 17 per group. Follow-up post-treatment and 0 month, 1 month, 4 months post randomization. rTMS vs sham: BMI, ED symptoms, mood, quality of life. Preliminary evidence for therapeutic potential of rTMS.

GLP-1 Agonists

- Richards (2023) Glucagon-like peptide-1 (GLP1) analog semaglutide has profound effects on central satiety signaling leading to reduced food intake, and has been approved for the treatment of obesity based on its efficacy and safety profile.
- This open-label study examined the effects of semaglutide on Binge Eating Scale (BES) scores in individuals with BED. Patients were divided into three groups: those prescribed semaglutide, those prescribed either lisdexamphetamine or topiramate, and those prescribed a combination of semaglutide with lisdexamphetamine or topiramate.
- *Results:* Patients receiving semaglutide only exhibited greater reductions in BES scores compared to the other groups. Combined pharmacotherapy with both semaglutide and the other anti-obesity medications did not result in greater reductions in BES scores compared to the semaglutide-only group. Findings were similar in patients with moderate/severe BED, as well as the full sample. *Conclusion:* The therapeutic effects of semaglutide in binge eating disorder warrant further investigation.
- Bartel 2024 It is possible that GLP-1As could maintain, worsen, or improve ED symptoms. Review of the limited literature on GLP-1As and ED symptoms, recommends future research, and provides clinicians with a guide for discussing GLP-1As with ED clients.

Successful treatment of binge eating disorder with the GLP-1 agonist semaglutide: A retrospective cohort study

Jesse Richards a,*, Neha Bang a, Erin L. Ratliff b, Maria A. Paszkowiak a, Zhamak Khorgami a, Sahib S. Khalsa c, W. Kyle Simmons 2023

- Open-label study - semaglutide on Binge Eating Scale (BES) scores in individuals with BED.
- Patients were divided into three groups:
  - prescribed semaglutide
  - prescribed either lisdexamphetamine or topiramate
  - prescribed a combination of semaglutide with lisdexamphetamine or topiramate.
- Results: Patients receiving semaglutide only exhibited greater reductions in BES scores compared to the other groups.
- Combined pharmacotherapy with both semaglutide and the other anti-obesity medications did not result in greater reductions in BES scores compared to the semaglutide-only group.
- Findings were similar in patients with moderate/severe BED, as well as the full sample.
- Conclusion: The therapeutic effects of semaglutide in binge eating disorder warrant further investigation.
- Effect on psychiatric co-morbidity not included in paper

Efficacy of deep brain stimulation for the treatment of anorexia nervosa: a systematic review and network meta-analysis of patient-level data

Shaffer 2023

- Deep brain stimulation (DBS) has been approved as a therapy for movement disorders and OCD.
- DBS has been studied in patients with AN. Several stimulation locations have been tested without a clear indication of the best
- region. In this systematic review and network meta-analysis, the authors used patient-level data to identify stimulation
- targets with the greatest evidence for efficacy in increasing body mass index (BMI).
- Systematic search was performed on or before August 4, 2022, using PubMed/MEDLINE, Ovid, and Scopus. Articles were included if patient-level data were presented, patients were diagnosed with AN and treated with DBS, and 6 months or more of postoperative follow-up data were reported.
- RESULTS Eleven studies consisting of 36 patients were included. At the time of surgery age was
- 38.07 (SD 11.64) years and BMI was 12.58 (SD 1.4) kg/m2 .
- After 6 months of DBS, a significant difference in percentage change in BMI was found between the nucleus accumbens and subcallosal cingulate cortex (SCC) (SMD 0.78; 95% CI 0.10, 1.45) and between the SCC and ventral anterior limb of the internal capsule (SMD −1.51; 95% CI −2.39, −0.62). Similarly, at 9–12 months, a significant difference in percentage change in BMI was found between the SCC and ventral anterior limb of the internal capsule (SMD −1.18; 95% CI −2.21, −0.15).
- With hierarchical ranking, this study identified SCC as the most supported stimulation location for BMI change at 6 and 9–12 months
- CONCLUSIONS Several DBS targets have been tested for AN, and this study identified the SCC as the most supported
- region for BMI change. However, further studies with blinded on/off periods are necessary to confirm this finding.

Treatment studies with cannabinoids in anorexia nervosa: a systematic review Rosager 2020

- Cannabis has been known to cause physical effects on the human body, including increasing appetite, which may be beneficial in the treatment of AN.
- Objective To systematically review the literature for evidence of an effect of cannabinoids on (1) weight gain, and (2) other outcomes, in AN. There were 1288 studies identified and after thorough review and exclusion of copies, 4 studies met the inclusion criteria. Three studies used the same AN population and utilized data from one original study, leaving only two original studies. Both of these were Randomized Controlled Trials that explored the effects of delta-9-tetrahydrocannabinol (Δ9-THC) or dronabinol in AN, where one study was properly designed and powered and showed a weight increase of an added 1 kg over 4 weeks over placebo.
- Discussion and conclusion There are few studies and the level of evidence is low. The only properly designed, low bias and highly powered study found a weight increasing effect of dronabinol in AN, while the other, using Δ9-THC at a high dose, found no effect and where the dose may have counteracted the weight gaining effects due to adverse events.
- More research on cannabinoids in anorexia nervosa is warranted, especially its effects on psychopathology.

SUMMARY

- Limited options for treatment
  - Few controlled trials with long term follow-up
  - Etiologic perceptions – Lack consensus of contributory mechanisms
  - Few Academic ED programs – majority of care private for profit programs
  - AN patients: Limited motivation, cooperation
  - Limited funding (NIH, pharma industry)
  - Confounds
    - State-related (nutrition, weight), age, and chronicity
    - Subgroup and comorbidity – need large sample sizes and multicenter collaboration

Contributions to Poor Outcome

- **Anxiety in AN is associated with increased symptoms**: (Lilenfeld 1998, Dellava 2010, Raney 2008, Bloss 2011, Steinglass 2014)
  - lower BMI and greater caloric restriction
  - greater psychopathology
  - poor outcomes
- **Dysregulated Eating Behavior** (Kaye 2020; Monteleone 2018; Holsen 2012)
  - Aberrant Eating: reduced motivation and reward, increased inhibition, altered interoception

Psychedelics in the treatment of eating disorders: Rationale and potential mechanisms (case reports, series – not controlled trials)

Calder, Mock. Friedli, Pasi, Hasler 2023

Psychedelic-assisted therapy has recently shown potential in the treatment of several common comorbidities of eating disorders, including mood disorders, post-traumatic stress disorder, and substance use disorders.

Review of preliminary data on the efficacy of psychedelic-assisted therapy in people with anorexia nervosa, bulimia nervosa, and binge eating disorder (studies and case reports) of psychedelic-assisted therapy MDMA, psilocybin, and ayahuasca.

We find preliminary evidence that psychedelic-assisted therapy may be effective in the treatment of anorexia nervosa and bulimia nervosa, with very little data available on binge eating disorder

Speculates that psychedelics could help with co-morbid disorders

Treatment of Co-morbid OCD and AN

Lewin, Menzel, Strober 2013; Simpson 2013

- OCD complicates AN presentation, prognosis, assessment, and intervention
- OCD symptoms in individuals with eating disorders confers greater severity and persistence of eating disorder symptoms (Jimenez-Murcia et al., 2007; Milos, Spindler, Ruggiero, Klaghofer, & Schnyder, 2002) and increased overall levels of associated anxiety and depression (Sallet et al., 2010)
- Few treatment studies have targeted individuals with comorbid OCD and AN
- OCD in AN often not respond to Serotonin specific meds
- Multi-modal (Simpson 2013): CBT + exposure and response prevention (ERP) + meds: Reported significant decreases in OCD severity, ED severity, and depression. BN respond better than AN.

Why so few RCT in AN?

- No proven effective medications for AN, high mortality and chronicity
- Few controlled (placebo) trials in AN
- Very few studies assess response of common co-morbid disorders
- Study confounds
  - Resistance to engaging in treatment
  - State of nutrition and weight
  - Subtypes of AN
  - Probably requires multi-center collaborations to have sufficient n

Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo-controlled, double-blind trial.

Fluoxetine Bulimia Nervosa Collaborative Study Group 1992

- 8-week, double-blind trial comparing fluoxetine hydrochloride (60 and 20 mg/d) with placebo
- 387 bulimic women treated on an outpatient basis.
- Fluoxetine at 60 mg/d proved superior to placebo in decreasing the frequency of weekly binge-eating and vomiting episodes at end point.
  - Fluoxetine at 20 mg/d produced an effect between that of the 60-mg/d dosage and that of placebo.
- Depression, carbohydrate craving, and pathologic eating attitudes and behaviors also improved significantly with fluoxetine
  - The higher dosage again showing a more robust effect than the lower dosage.
- Adverse events (i.e., insomnia, nausea, asthenia, and tremor) occurred significantly more frequently with fluoxetine (60 or 20 mg/d) than with placebo.
- FDA approved 60mg/day fluoxetine for treatment of BN

Efficacy of Lisdexamfetamine in Adults With Moderate to Severe Binge-Eating Disorder, A Randomized Clinical Trial

Hudson, McElroy, Ferreira-Cornwell, Radewonuk, Gasior, JAMA Psychiatry 2017

- Multinational, phase 3, double-blind, placebo-controlled, randomized withdrawal study, 418 participants at 49 clinical research study sites f
- Eligible adults met DSM-IV-R binge-eating disorder criteria and had moderate to severe binge eating disorder (3 binge-eating days per week for 14 days before open-label baseline;
  - Clinical Global Impressions–Severity [CGI-S] scores 4 [moderate severity] at screening and open-label baseline).
- Following a 12-week, open-label phase (dose optimization, 4 weeks [lisdexamfetamine dimesylate, 50 or 70 mg]; dose maintenance, 8 weeks), lisdexamfetamine responders (1 binge eating day per week for 4 consecutive weeks and CGI-S scores 2 at week 12) were randomized to placebo or continued lisdexamfetamine during a 26-week, double-blind, randomized withdrawal phase.
- Of the 418 participants enrolled in the open-label phase of the study, 411 (358 [87.1%] women; mean [SD] age, 38.3 [10.4] years) were included in the safety analysis set.
- Of 275 randomized lisdexamfetamine responders (placebo, n = 138; lisdexamfetamine, n = 137),
- the observed proportions of participants meeting relapse criteria were 3.7% (5 of 136) for lisdexamfetamine and 32.1% (42 of 131) for placebo. Lisdexamfetamine demonstrated superiority over placebo on the log-rank test (χ 2
- for time to relapse; the hazard ratio, for lisdexamfetamine vs placebo, was 0.09 (95% CI, 0.04-0.23).
- The treatment-emergent adverse events observed were generally consistent with the known profile of lisdexamfetamine.
- Risk of binge-eating relapse over 6 months was lower in participants continuing lisdexamfetamine than in those randomized to placebo.

SUMMARY

- Limited research
  - Only BED and BN have FTC approved medications
  - Few RCT
  - Pathophysiology of ED and comorbid disorders poorly understood and controversial
  - Little data on comorbid disorder response or comparison of medications
  - Clinical impressions of effective meds
    - Aripiprazole AN
    - Mirtazapine ARFID
- Challenges
  - OCD, PTSD, suicide risk, personality and temperament, treatment resistance