Brief description of patient problem/setting (summarize the case very briefly)
A 19 y/o female presents to the emergency department with fatigue, depression and significantly low BMI.

Search Question:
Do antidepressants help treat and prevent relapse in those diagnosed with anorexia nervosa?

PICO search terms:

P	I	C	O
Anorexia nervosa	Antidepressants		Efficacy
Anorexic	SSRIs		Relapse prevention
AN	Pharmacological treatment		BMI improvement
Eating disorders			Adverse events

Results found:
PubMed:
- Antidepressants for anorexia nervosa (Best Match, Review) - 152
- Antidepressants for treatment of anorexia (Best Match) – 199

Google Scholar:
- Antidepressants for treatment of anorexia (range 2015-2020, sort by relevance) – 13,600
- Relapse prevention of anorexia (range 2015-2020, sort by relevance) – 13,100

Cochrane:
- Antidepressants for treatment of anorexia nervosa - 87

1. Citation: Role of antidepressants in the treatment of adults with anorexia nervosa. Marvanova M, et al. Ment Health Clin. 2018. PMID: 29955558 Free PMC article. Review.
Full article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6007635/pdf/i2168-9709-8-3-127.pdf
Type of article:

Systematic Review

Abstract:
Introduction: Anorexia nervosa (AN) is a severe psychiatric disorder that is difficult to treat and is associated with frequent relapses and high mortality rates. Psychiatric symptomatology (eg, depression, anxiety, obsessive-compulsive disorder/behaviors) are common comorbidities. This review provides current information about safety and efficacy of antidepressant therapy for management of AN in adults.

Methods: A literature review of randomized controlled trials, open-label studies, and case reports with adults or adults/adolescents was conducted. PubMed and Medline were searched using anorexia management and treatment, antidepressants, selective serotonin reuptake inhibitors (SSRIs), fluoxetine, sertraline, citalopram, and mirtazapine in AN, relapse prevention in AN, and psychotropic medications in AN.

Results: The role and utility of antidepressants in AN were published in double-blind, placebo-controlled studies; open-label trials; and a retrospective study. Antidepressants should not be used as sole therapy for AN although their use for confounding symptomatology makes discerning efficacy difficult as they are given together with other therapies. Neurobiological changes due to starvation and AN itself complicate results interpretation. For safety, tricyclic antidepressants and monoamine oxidase inhibitors are not recommended, and bupropion is contraindicated. Use of SSRIs during acute treatment lacks efficacy. Use of SSRIs-primarily fluoxetine and to some extent citalopram, sertraline, or mirtazapine-may aid in relapse prevention and improvement of psychiatric symptomatology in weight-restored anorexic patients.

Discussion: Health care professionals should use clinical judgment regarding fluoxetine or possibly citalopram, sertraline or mirtazapine as adjunctive treatment to psychotherapy for relapse prevention, improvement of depressive and anxiety symptoms, and/or obsessive-compulsive behaviors unresolved with nutritional rehabilitation and psychotherapy.

2. Citation:
Psychopharmacological options for adult patients with anorexia nervosa.
Miniati M, et al. CNS Spectr. 2016. PMID: 26145463 Review.

Type of article:
Systematic review

Full article:
https://dacemirror.sci-hub.do/journal-article/e5079d5465abb17d4270c3860364141c/miniati2015.pdf

Abstract:
The aim of this review was to summarize evidence from research on psychopharmacological options for adult patients with anorexia nervosa (AN). Database searches of MEDLINE and PsycINFO (from January 1966 to January 2014) were performed, and original articles published as full papers, brief reports, case reports, or case series were included. Forty- one papers were screened in detail, and salient

characteristics of pharmacological options for AN were summarized for drug classes. The body of evidence for the efficacy of pharmacotherapy in AN was unsatisfactory, the quality of observations was questionable (eg, the majority were not blinded), and sample size was often small. More trials are needed, while considering that nonresponse and nonremission are typical of patients with AN.

3. Citation:
Pharmacological treatment of acute-phase anorexia nervosa: Evidence from randomized controlled trials
E Cassioli, C Sensi, E Mannucci… - Journal of …, 2020 - journals.sagepub.com

Pdf:
https://sci-hub.do/downloads/2020-05-26/d6/10.1177@0269881120920453.pdf

Type of article:
Meta-Analysis

Abstract:
Background: Anorexia nervosa (AN) is the psychiatric disorder with the highest mortality rate, with a standard mortality ratio of 5.86. Despite the large use of psychotropic drugs in the clinical setting, Food and Drug Administration has not approved any psychoactive treatment for AN.

Aims: The aim of this study was to perform an updated systematic review and meta-analysis of published randomized controlled trials (RCTs) investigating psychopharmacological treatment in acute-phase AN.

Methods: The present paper follows the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. An extensive literature search was performed. All RCTs enrolling patients with acute-phase AN, comparing at least one psychotropic drug with another drug, placebo, treatment-as-usual or no treatment were included. The main outcome was the effect of psychoactive drugs on body mass index (BMI); data on psychopathological outcomes were also collected when available.

Results: A total of 19 RCTs met all specified criteria. Of these, 11 were excluded from quantitative analyses. Of the eight studies included in the meta- analyses, five reported data on BMI, showing no significant difference between olanzapine and placebo for weight recovery. No significant result was found for AN psychopathology, depressive and anxious symptoms for any of the molecules studied.

Conclusions: RCTs published in this field display methodological biases, low sample sizes and short follow-up periods. Further research efforts are needed in this field as no evidence has been demonstrated for the use of any psychotropic drug in acute-phase AN neither for weight recovery, nor for comorbid psychiatric symptoms.

4. Citation
Antidepressants for anorexia nervosa.
Claudino AM, et al. Cochrane Database Syst Rev. 2006. PMID: 16437485 Review.

PDF:
https://zero.sci-hub.do/2640/69b1ffa3f0a4b3a9282ee68ce4623893/claudino2006.pdf

Type of article:
Systematic review

Abstract:
Background: Anorexia Nervosa (AN) is an illness characterised by extreme concern about body weight and shape, severe self-imposed weight loss, and endocrine dysfunction. In spite of its high mortality, morbidity and chronicity, there are few intervention studies on the subject.

Objectives: The aim of this review was to evaluate the efficacy and acceptability of antidepressant drugs in the treatment of acute AN.

Search strategy: The strategy comprised of database searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, MEDLINE (1966 to April 28th, 2005), EMBASE (1980 to week 36, 2004), PsycINFO (1969 to August week 5, 2004), handsearching the International Journal of Eating Disorders and searching the reference lists of all papers selected. Personal letters were sent to researchers in the field requesting information on unpublished or in-progress trials.

Selection criteria: All randomised controlled trials of antidepressant treatment for AN patients, as defined by the Diagnostic and Statistical Manual, fourth edition (DSM-IV) or similar international criteria, were selected.

Data collection and analysis: Quality ratings were made giving consideration to the strong relationship between allocation concealment and potential for bias in the results; studies meeting criteria A and B were included. Trials were excluded if non-completion rates were above 50%. The standardised mean difference and relative risk were used for continuous data and dichotomous data comparisons, respectively. Whenever possible, analyses were performed according to intention-to-treat principles. Heterogeneity was tested with the I-squared statistic. Weight change was the primary outcome. Secondary outcomes were severity of eating disorder, depression and anxiety symptoms, and global clinical state. Acceptability of treatment was evaluated by considering non-completion rates.

Main results: Only seven studies were included. Major methodological limitations such as small trial size and large confidence intervals decreased the power of the studies to detect differences between treatments, and meta-analysis of data was not possible for the majority of outcomes. Four placebo-controlled trials did not find evidence that antidepressants improved weight gain, eating disorder or associated psychopathology. Isolated findings, favouring amineptine and nortriptyline, emerged from the antidepressant versus antidepressant comparisons, but cannot be conceived as evidence of efficacy of a specific drug or class of antidepressant in light of the findings from the placebo comparisons. Non-completion rates were similar between the compared groups.

Authors' conclusions: A lack of quality information precludes us from drawing definite conclusions or recommendations on the use of antidepressants in acute AN. Future studies testing safer and more tolerable antidepressants in larger, well designed trials are needed to provide guidance for clinical

practice.

5. Citation **Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial** B Timothy Walsh et al. JAMA 2006 Jun 14; 295(22):2605-12.
PDF:
Type of article: Randomized control trial
Abstract: Objective To determine whether fluoxetine can promote recovery and prolong time-to-relapse among patients with anorexia nervosa following weight restoration. Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial. From January 2000 until May 2005, 93 patients with anorexia ner-vosa received intensive inpatient or day-program treatment at the New York State Psychiatric Institute or Toronto General Hospital. Participants regained weight to a minimum body mass index (calculated as weight in kilograms divided by the square of height in meters) of 19.0 and were then eligible to participate in the randomized phase of the trial. Interventions Participants were randomly assigned to receive fluoxetine or placebo and were treated for up to 1 year as outpatients in double-blind fashion. All patients also received individual cognitive behavioral therapy. Main Outcome Measures The primary outcome measures were time-to-relapse and the proportion of patients successfully completing 1 year of treatment. Results Forty-nine patients were assigned to fluoxetine and 44 to placebo. Similar percentages of patients assigned to fluoxetine and to placebo maintained a body mass index of at least 18.5 and remained in the study for 52 weeks (fluoxetine, 26.5%; placebo, 31.5%; P=.57). In a Cox proportional hazards analysis, with pre randomization body mass index, site, and diagnostic subtype as covariates, there was no significant difference between fluoxetine and placebo in time-to-relapse (hazard ratio, 1.12; 95% CI, 0.65-2.01; P=.64). Conclusions This study failed to demonstrate any benefit from fluoxetine in the treatment of patients with anorexia nervosa following weight restoration. Future efforts should focus on developing new models to understand the persistence of this illness and on exploring new psychological and pharmacological treatment approaches.

Author; Reference	Level of evidence	Patient Group/ Data collection	Outcomes studied	Key Findings	Limitations/ Biases

Role of antidepressants in the treatment of adults with anorexia nervosa. Marvanova M, et al	Systematic review	13 studies with 345 participants diagnosed with AN The study population was adults only or adults and adolescents combined Studies were RCTs, case reports, case studies, and an open-label study	Weight restoration/ maintenance Relapse prevention	Antidepressants should only be used as adjunctive treatment to nutrition and psychotherapy. There is little evidence to support the use of SSRIs or mirtazapine during an acute AN treatment phase. The data is inconclusive whether SSRIs will benefit patients with AN during maintenance treatment Selective serotonin reuptake inhibitors, as adjunctive treatment, may offer relapse prevention and/or improvement of concurrent psychiatric symptoms	Some studies that were used had a very small number of participants (ex: 5 participants)
Psychopharmacological options for adult patients with anorexia nervosa. Miniati M, et al.	Systematic review	41 studies were included. 17 studies were RCTs The number of participants varied between	Improvement of depressive symptoms Weight gain/ maintenance in AN patients Relapse rate	Research found that there is no clear evidence supporting the use of SSRIs in AN.	Limitations included small sample sizes, differences in study protocol, research conducted in single centers, and clinical

		1 and 93, 25 studies were conducted on inpatients (594 patients) and 15 studies on outpatients (321 patients). The age range was 18-50 and all patients were diagnosed with AN (different subtypes).		With regards to fluoxetine, the results were controversial. The first trial was a small, open study in 6 patients with chronic, refractory AN. The authors found an improvement of depressive symptoms and a significant weight gain. Patients tolerated fluoxetine even at the higher dosages. In another study, there were no differences found between fluoxetine and placebo in 2 studies conducted in AN-R inpatients. In a third study, patients receiving fluoxetine showed a significantly	rather than statistical interpretation of results. There was diagnostic heterogeneity, ethical issues in treatment, and challenges in the organization of a mid-term/ long-term follow-up. The majority of the RCTs were not blinded.

				lower rate of relapse than those randomized to placebo.	
Pharmacological treatment of acute-phase anorexia nervosa: Evidence from randomized controlled trials E Cassioli, C Sensi, E Mannucci	Meta-analysis	8 RCTs on patients with acute phase AN	The effects of psychoactive drugs compared with other drugs, placebo, TAU (treatment as usual) or no treatment, on BMI and psychopathological features	Three studies reported data on antidepressant drugs, specifically fluoxetine. They reported no significant effect on any outcomes evaluated, including ED psychopathology, general psychopathology and BMI recovery. Another study found that citalopram had a positive effect on depressive and OCD symptoms but no effect on ED specific features and BMI.	The RCTs showed methodological biases, low sample sizes and short follow-up periods
Antidepressants for anorexia nervosa. Claudino AM, et al	Systematic review	7 RCTs with 178 patients lasting 4 weeks comparing any	End of treatment BMI, number of patients achieving	No evidence of any effect on weight gain was found for antidepressants	Small sample sizes and large confidence intervals were some

		antidepressant drugs to placebo, or other antidepressant drug	target weight or weight within a normal range, mean rate of weight gain, number of days to achieve ideal weight, and depressive symptoms	combined with other interventions when compared to placebo. Fluoxetine compared to placebo showed no significant difference in weight gain.	limitations. The placebo controlled studies were short in length (mean duration about 5 weeks and no follow-up period).
Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial B Timothy Walsh et al	Randomized control trial	Randomized, double blind, placebo controlled trial. 49 patients were assigned to fluoxetine and 44 to placebo and were treated up to 1 year as outpatients. Participants were female between the ages of 16 and 45 years. Patients also received CBT	Primary outcome measured were time to relapse and the proportion of patients completing 1 year of treatment	No significant differences between fluoxetine and placebo groups in BMI or in measures of psychological state. As for time to time relapse, there was no significant difference between the fluoxetine and placebo groups.	The study examined the use of fluoxetine at a particular stage of illness and in conjunction with a structured psychological treatment. Antidepressant s might have an effect at other stages of illness. The sample size was also small.

Cassioli et al> Miniati et al > Marvanova et al > Walsh et al > Claudino et al

Conclusions

Marvanova et al concluded that there is little evidence to support the use of SSRIs or mirtazapine during an acute AN treatment phase. It is also inconclusive whether SSRIs will benefit patients with AN during maintenance treatment. SSRIs, as adjunctive treatment, may offer relapse prevention and/or improvement of concurrent psychiatric symptoms.

Miniati et al concluded that there is no clear evidence supporting the use of antidepressants in AN but they may improve anxiety, irritability, mood lability, and depressive symptoms that can complicate the

course of AN. Antipsychotics, besides olanzapine, produce no significant effect on the core symptoms of AN.

Cassioli et al concluded that antidepressants, particularly fluoxetine, had no significant effect on any outcomes evaluated, including ED psychopathology, general psychopathology and BMI recovery. It was also concluded that citalopram had a positive effect on depressive and OCD symptoms but no effect on ED specific features and BMI. There was no difference between olanzapine and placebo for weight recovery.

Claudino et al concluded that there was a lack of quality evidence to determine the efficacy of antidepressants in the acute phase of anorexia nervosa. There was no evidence of any effect on weight gain with antidepressants combined with other interventions when compared to placebo. Fluoxetine compared to placebo showed no significant difference in weight gain.

Walsh et al concluded that there was no significant difference between fluoxetine and placebo in time to time relapse. The study failed to demonstrate any benefit from fluoxetine in the treatment of AN following weight restoration.

Clinical Bottom Line

Weight of evidence:

Marvanova et a was a systematic review of 13 studies with 345 participants diagnosed with AN.

Miniati et al was a systematic review of 41 studies. 17 studies were RCTs. The number of participants varied between 1 and 93, 25 studies were conducted on inpatients (594 patients) and 15 studies on outpatients (321 patients).

Cassioli et al was a meta-analysis of 8 RCTs with patients diagnosed with acute-phase AN. The studies compared at least one psychotropic drug with another drug, placebo, treatment as usual or no treatment.

Claudino et al was a systematic review of 7 RCT. There were a total of 178 patients diagnosed with acute phase AN. The study compared antidepressants with placebo or other antidepressants.

Walsh et al was RCT of 93 patients in total. The study compared the use of fluoxetine with placebo for the treatment of anorexia nervosa in an outpatient setting.

Magnitude of any effects:

Using the evidence from these studies, the use of antidepressants to help treat anorexia nervosa and prevent relapse is unsupported, but it is shown to improve psychiatric symptoms such as depression and anxiety.

Clinical significance

Anorexia nervosa is a potentially fatal psychiatric condition that is among the top leading causes of disability in young adults. Currently, psychological treatments remain the first-line therapy for anorexia nervosa, which includes cognitive behavioral therapy, Maudsley anorexia nervosa treatment for adults,

and specialist supportive clinical management. Although the FDA has not approved any psychoactive treatments for AN, The American Psychiatric Association's guidelines recommend using psychoactive drugs as adjunctive therapy when AN is associated with other psychiatric symptoms, such as depression, OCD or anxiety. According to research, antidepressants (SSRIs) have not reported any significant efficacy on AN outcomes, BMI improvement or weight maintenance. However, antidepressants may be beneficial in relapse prevention and psychiatric symptoms such as depression and anxiety. Further research and meta-analyses are needed that focuses on neurobiological studies in order to identify possible pharmaceutical targets. In addition, further trials with larger samples and a longer follow up are needed.