LUND UNIVERSITY

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Pharmacological treatment of the core symptoms of Anorexia nervosa – a systematic literature review

[Farmakologisk behandling av huvudsymptomen vid Anorexia nervosa – en systematisk litteraturöversikt]

Master thesis

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Abstract

Background/Aim: Anorexia nervosa (AN) is a serious psychiatric disorder with one of the highest mortality rates of all psychiatric diagnoses. Today there is no approved pharmacological treatment of Anorexia Nervosa. The aim of this study is to investigate if there is some effective and safe pharmacological treatment of the core symptoms of Anorexia nervosa (AN) by conducting a systematic review. There is no newly published systematic review with the same aim and methodological approach.

Methods: A systematic review was conducted by searching in the following databases: PubMed, Embase and PsycINFO using the PICO strategy. Randomized controlled studies from the latest 10 years were included. Primary outcome measurements were weight, BMI (Body mass index) and caloric intake and secondary was ED (eating-disorder psychopathology). The safety of the interventions was carefully evaluated. Two independent reviewers screened and performed the quality assessment using the GRADE approach. 12 studies were included.

Results: Only four studies presented significant results of weight gain/BMI increase: dronabinol (1), olanzapine (2), D-Cycloserine in enhancement of exposure therapy (1). Oxytocin (1) had a positive impact on ED (eating disorder) psychopathology. The efficacy was generally modest. Overall, the studies had small sample sizes and a high level of heterogeneity. The weighted quality was very low mostly due to high drop-out rates which is a common problem in this population. All the drug therapies were safe and well tolerated and no adverse events were reported.

Conclusion: The significant positive results need to be confirmed in larger high-quality long-term studies. Both the results regarding the weighted low quality of the included studies and the modest results regarding efficacy and the safety of the medications was overall in accordance with other systematic reviews regarding pharmacological treatment of AN.

Populärvetenskaplig sammanfattning

Bakgrund

Anorexia nervosa (AN) är en av de psykiatriska sjukdomarna med högst dödlighet. Trots att första fallet upptäcktes redan år 1689 så finns det idag ännu inte någon tillräckligt effektiv behandling, i alla fall inte för vuxna. Viktfobi och en överdriven kroppsfixering utmärker sjukdomen. AN är vanligast bland flickor i tonåren och nästan 3% av alla tonåringar är drabbade. En ökning i antal personer som insjuknar har setts senaste åren och Covid-19 pandemin verkar ha lett till ytterligare incidensökning.

Det är inte helt klarlagt vad AN beror på men en kombination av neurobiologiska, psykologiska och omgivningsfaktorer tros ligga bakom. Ofta föregås sjukdomen av en bantningsperiod och inte sällan en stressande livshändelse. Familjebaserad behandling har visat sig vara den mest effektiva behandlingsformen för barn och ungdomar. För vuxna finns inte lika starkt stöd för någon enskild behandling men kognitiv beteendeterapi och psykoterapi är exempel på behandlingsformer som kan prövas. Många lider av sjukdomen under många år, återfall är vanligt och livskvaliteten är ofta nedsatt. Ur ett hälsoekonomiskt perspektiv medför sjukdomen höga kostnader. Det är vanligt att den drabbade även har samsjuklighet i form av depression, ångest eller tvångssyndrom. Följdtillstånd såsom benskörhet och andra kroppsliga symptom är vanliga. Det är viktigt för framtidsprognosen att snabbt få hjälp och vända viktnedgången. Eftersom de bakomliggande orsakerna inte är helt klarlagda är det inte konstigt att dagens behandlingsformer inte är så effektiva. Behovet av nya effektiva behandlingsmetoder är stort.

Det finns idag inga godkända mediciner för AN och det saknas nyare systematisk litteraturöversikt gällande potentiella sådana med samma syfte och metodologiska ansats som denna systematiska litteraturstudie.

Syfte

Syftet med detta examensarbete är att undersöka om det finns någon effektiv och säker farmakologisk behandling av huvudsymptomen vid AN genom att sammanställa det vetenskapliga underlaget i en systematisk litteraturöversikt för att utvärdera resultatet av enskilda studier. Denna systematiska litteraturöversikt är tänkt att kunna användas av såväl sjukvårdspersonal som arbetar med denna patientgrupp som av forskare för framtida forskning.

Metod

Baserat på syftet sattes sökkriterier upp och sökningar i de medicinska/psykiatriska databaserna PubMed, Embase och PsycINFO påbörjades. Endast randomiserade kontrollerade studier och kontrollerade kliniska studier inkluderades för att öka tillförlitligheten. De senaste 10 åren (2011.01.01-2021.02.01) valdes för att endast inkludera senaste vetenskapen. Efter att ha sökt igenom samtliga databaser och erhållit totalt 96 träffar (inkl två artiklar funna via kedjesökning i publicerade litteraturöversikter) påbörjades urvalsprocessen baserat på de inklusions- och exklusionskriterier som tidigare satts upp. Två granskare selekterade oberoende av varandra fram de artiklar som uppfyllde kriterierna och i de fall olika åsikter fanns enades vi och vid behov rådfrågades en tredje granskare. Därefter genomfördes en kvalitetsgranskning av artiklarna av två granskare oberoende av varandra. Slutligen inkluderades 12 artiklar i denna systematiska litteraturöversikt.

Resultat

Av de 12 studierna som inkluderades visade fyra positiva signifikanta resultat gällande viktuppgång/BMI (Body Mass Index) för den grupp som blivit tilldelad läkemedlet jämfört med placebo: dronabinol (1), olanzapine (2), D-Cycloserine i kombination med exponeringsterapi (1). Endast en studie fann signifikant förbättring vad gäller typiska

ätstörningssymptom: oxytocin (1) jämfört med placebo. Även om effekterna i de flesta fall inte var så stora så kan även små viktuppgångar göra stor skillnad för den drabbade, särskilt i det akuta skedet då hälsan riskerar att påverkas allvarligt. Enstaka biverkningar kunde noteras men inga allvarliga händelser kopplade till de undersökta medicinerna kunde konstateras. Detta behöver dock bekräftas i framtida långtidsstudier.

Kvaliteten på artiklarna var generellt låg med några få undantag. Den låga kvaliteten berodde framförallt på att många av deltagarna hoppade av i förtid från studierna vilket är ett välkänt problem i denna patientgrupp. Det är generellt svårt att rekrytera anorektiker till farmakologiska studier med viktuppgång som intention så många av de inkluderade studierna har lågt antal studiedeltagare. Den sammanvägda kvaliteten av studierna bedömdes som väldigt låg vilket innebär att vi inte kan vara säkra på effekterna som studierna presenterat och att den sanna effekten sannolikt skiljer sig från den presenterade.

Slutsats

Resultaten visade att det finns några potentiella läkemedel (dronabinol, D-Cycloserine, olanzapine och oxytocin) som skulle kunna vara till nytta som behandling av huvudsymptomen vid AN. Den generellt låga kvaliteten på studierna i kombination med få observationer innebär dock att de resultat som presenterats måste tolkas med försiktighet och behöver upprepas med ett större antal studiedeltagare och högre kvalitet på studierna för att kunna dra säkra slutsatser och ge rekommendationer. Effekten av dessa läkemedel verkade inte vara tillräckligt stor för att dessa ska kunna användas som ensam behandling av anorexia utan bör troligtvis kombineras med annan behandling.

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1. BACKGROUND

1.1 Anorexia nervosa

Even though the first described case of Anorexia Nervosa (AN) was as early as 1689 there is up till today still no effective treatment, at least not for adults.[1-2] AN is one of the most deadly disorders of all psychiatric disorders with a standardized mortality ratio (SMR) of 5.86.[3] 20% of all patients diagnosed with AN get chronically long-term ill.[4]

Another problem is the high relapse rate that according to a systematic review is as high as 31% and even higher the first year after discharge.[5] Around 1/3 fail to recover and are still ill after 22 years. In AN it's not unusual that the recovery takes many years and around 1/3 recovers after 9 years sickness, a strong reason not to implement palliative care for people with eating disorders which is often the case. Time is crucial because early recovery increases the chances of long-term recovery.[6]

From a health economic perspective AN is associated with high costs of healthcare and loss of income.[7] For the victims of the disease, their families and caregivers the quality of life is reduced.[8]

1.1.1 Prevalence and incidence

AN is a serious psychiatric disease with a point prevalence of 2.8% for women and 0.3% for men with a peak onset at the median age of 12.3.[9-10] The incidence is 1/10 in men compared to women. According to Javaras KN et al. (2015), the incidence increased in Sweden from year 2000 and is between 4.7 and 7.7 yearly new cases per 100 000 citizens.[11-12] The incidence increase for women in all ages (both in- and outpatients) was also confirmed by a systematic review and meta-analyze from 2020 including 31 articles from different

countries.[13] It seems like the COVID-19 pandemic has contributed to an additional increase, at least in Australia.[14]

1.1.2 Diagnostic criteria

The ICD classification and the DSM diagnostic systems are the foundation for the diagnostic criteria.[15] According to the Diagnostic and Statistical Manual of Mental Disorders DSM-V (APA 2013) the core symptoms of AN are a reduced body weight due to restrictive food intake, "intense fear of gaining weight" and a disturbed body perception or lack of insight of the low body weight in relation to age, sex and physical health (figure 1).[16] In ICD-10 (International Classification of Diseases-10) amenorrhea is added to the diagnostic criteria (World Health Organization 1992) even though it does not include males and females taking oral contraceptives.[17-18] "DSM-5 Changes: Implications for Child Serious Emotional Disturbance [Internet]" specifies the differences between DSM-IV and DSM-V.[19]

AN can be divided into two subtypes, the restrictive (AN-R) respectively the binge-eating/purging subtype (AN-BP). The restrictive type is characterized by dieting/fasting and/or excessive exercise while binge-eating or compensatory behavior (usually forced vomiting, laxatives and/or diuretics) is the main character of AN-BP.[20] Crossover between the subtypes is common according to a longitudinal follow-up.[12]

1.1.3 Pathophysiology

The complexity of AN's nature involves an interaction of neurobiological, psychological, and environmental factors but the pathophysiology is not entirely clear.[21-22] A stressful life event and dieting often precedes the onset of the disease.[23] According to a Swedish population-based study of twins the heredity of the disorder is approximately 56% (based on the DSM-IV criteria).[24] The microbiota-gut-brain axis is an appreciable research field and microbiota has

been suggested to have impact on cognitive ability, depression and stress responses.[25] All these complex behaviors is involved in AN.[26] The gut microbiota has been found to be altered in AN.[27]

According to a review from 2019 insula, striatum, dopamine circuitry and orbitofrontal cortex seem to be involved in the neurobiological pathogenesis of AN.[28] Evidence from several studies point at altered connectivity involving insula (involved in taste perception and body perception integration etc.).[29] Dorsal striatum has been proposed to be implicated in the brain response to choice of food in AN. Brain scans has demonstrated that the connectivity between striatum and frontal cortex activation inversely correlates with caloric food intake suggesting fronto-striatal involvement in forming a habit of food restriction behavior in AN.[30] Alterations in the dopaminergic reward system together with neuroendocrine changes such as leptin and ghrelin in the regulation of brain reward mechanisms, has also been found in AN. In addition to this, increased anxiety in AN is suggested to disrupt the ordinary mechanisms that drive eating behavior. Social interaction is an additional area where brain alterations has been found.[31] Disturbances in menstrual cycle and estrogen depletion in AN patients is associated with cognitive deficits.[32] Different substances mentioned under "Pharmacological treatment in AN" is also proposed to be involved in the pathogenesis of AN.

1.1.4 Comorbidity

Most of the people with AN also suffer from physical and psychiatric comorbidity. Anxiety and depression are common as well as ADHD, autism, self-harming behavior and sometimes abuse. Somatic symptoms involving almost all organs are frequently occurring. Heart complications, epileptic seizures and amenorrhea are some of the physical comorbidities found in AN.[33] Due to amenorrhea and starvation, osteoporosis often becomes a problem.[34]

1.1.5 Treatment

Today's treatment interventions for AN are not effective enough (at least not for adults), which the high number of relapse-rates (31% according to a meta-analysis from 2018) and high part long term sick patients suffering from AN indicates.[2,4,5] According to Läkemedelsboken the only treatment where some support is to be found is family-based therapy for adolescents and according to preliminary results CBT (Cognitive Behavioral Therapy) to avoid relapse in weight restored adults.[23] According to NICE (National Institute for health and Care Excellence) Clinical guidelines one of the following psychological treatments should be considered for adults suffering from AN: individual eating-disorder-focused Cognitive Behavioral Therapy (CBT-ED), Maudsley Anorexia Nervosa Treatment for Adults (MANTRA) or Specialist Supportive Clinical Management (SSCM).[35] In accordance with Läkemedelsboken, NICE Clinical Guidelines recommend anorexia-nervosa-focused family therapy for children and young people with AN.[23,35] A randomized controlled trial mentions the importance of early weight gain in family-based treatment to achieve a greater weight gain and remission.[36]

Anorectics often value their disease so much that it's a challenge to motivate them to treatment with high drop-out rates from treatment as a result.[37-38] People with severe and enduring AN often want to improve but it's hard for them to commit and devote themselves to recovery because the disease has become a crucial part of who they are.[39] Due the poor treatment outcome associated with AN, there is a need for more effective treatment.[2]

A review from 2018 emphasizes targeted brain-based interventions as emerging treatments. The authors point out cognitive remediation therapy, exposure therapy and non-invasive neuromodulation as promising emerging treatments.[40] TMS treatment is another relatively new treatment option for "treatment-resistant" cases of AN that is currently tested in an open-

label pilot study. Preliminary, this study indicates some positive effects on AN pathology and anxiety and seem to be safe in AN patients but needs to be further evaluated.[41] Virtual avatars is an innovative new tool to motivate patients to fulfill treatment and improve drop-out rates.[42]

1.2 Potential pharmacological treatment of AN

Today there is no pharmacological treatment approved by the Food and Drug Administration for AN.[43] According to NICE Clinical Guidelines and Läkemedelsboken pharmacological treatment of AN should not be offered as a monotherapy.[23,35] According to a review from 2016, attempts to develop effective psychotropic medications have not been successful.[44] Different classes of medication have been suggested, for example atypical antipsychotics, hormones and vitamin-substitutes.

The value of psychopharmacological treatment could be limited during the severe catabolic phase of the disease.[23] There is no convincing evidence for SSRIs in AN and SSRIs are commonly known to be ineffective due to the malnutrition associated with the disorder.[45-46] If comorbid depression and/or OCD (obsessive compulsive disorder) treatment with SSRI could be indicated according to Läkemedelsboken. Anxiolytics and hypnotics during a limited time could be necessary if the problems are severe.[23]

In a newly published (May 2021) symposium of a randomized controlled trial (RCT), Psilocybin is declared to be involved in the bodily self-perception, suggested as a therapeutic target for AN.[47]

1.2.1 Atypical antipsychotics

There are metabolic side effects of the atypical antipsychotics that need to be considered.[48]

Olanzapine

Frank et al. suggest that disturbances in the dopaminergic system, either a decrease in the intrasynaptic DA (dopamine) concentrations or an increase in the D2/D3 receptor affinity or density, might explain the harm avoidance and high physical activity in AN.[49] Atypical antipsychotics, especially olanzapine which is a serotonin-dopamine-histamine antagonist, is known to have weight gain as a side effect.[50] The increased levels of dopamine in AN[49] and olanzapine's side effect of weight gain makes olanzapine a potential pharmacological treatment option in AN. According to a review from 2007, several studies have investigated this potential drug in AN and it presents positive results regarding weight gain and reduction of the psychological AN symptoms in response to olanzapine therapy.[51] This is a rather old review so new original studies have evolved since then and noteworthy is that many of the studies included in that review are not RCTs so the results should be considered with caution.[52]

Risperidone

Another atypical antipsychotic drug is the potent dopamine-serotonin-histamine antagonist called risperidone that has been suggested to have a positive effect on weight gain in AN according to case reports[44,53-55]. Only one RCT regarding risperidone as intervention for AN has been published recently and this one is included in this systematic review. Risperidone administrated to other patient populations is associated with a significant weight gain. This is often considered to be due to appetite increase followed by increased food intake but it might also be that risperidone has an impact on body metabolic rate.[56]

1.2.2 Hormones

Oxytocin

The nonapeptide and neuromodulator Oxytocin (OT) is another potential drug to enhance treatment outcome. It is produced by the hypothalamus, stored in the posterior pituitary and secreted into the portal blood stream and also straight to the limbic system binding to OT receptors. OT is involved in anxiety, learning, food consumption, fertility and social bond formation among other functions. Lower OT levels have been suggested to contribute to higher anxiety levels and social deficits in AN. Oxytocin is also suggested to be involved in the pathophysiology of AN but further research is needed to confirm this.[57] Could OT contribute to the core eating disorder psychopathology, motivation to change and weight gain in patients with AN?[58]

Dehydroepiandrosterone (DHEA)

The endogenic prohormone DHEA and its sulfate ester DHEAS act as adrenal sex steroid precursors that endogenously is converted to androgens and estrogens. There are conflicting and inconsistent reports regarding DHEA and DHEAS role in AN. According to some studies DHEA or DHEAS levels are decreased in AN but some studies only found decreased levels in patients on oral contraceptive treatment.[59-61-62] Some results point at a positive correlation between DHEA and bone mineral density (BMD) but some doesn't.[63-64] DHEA has several therapeutic aspects, for example on mood and depression.[65]

Ghrelin agonist

The orexigenic peptide hormone Ghrelin mainly produced in cells in the stomach, passes the blood-brain barrier and acts on the orexigenic center of hypothalamus and the nervus vagus and the appetite, hunger and gastric motility is stimulated.[66-67] Even though patients with AN has elevated levels of ghrelin their hunger is reduced in women with AN compared to healthy

controls.[68-69] This might be explained by ghrelin resistance or alterations in the intact versus degraded forms of ghrelin in women with AN.[70-71] Ghrelin resistance may lead to a lower appetite drive and restrictive eating according to Holsen et al.[70] An interaction between ghrelin and the dopaminergic reward system has also been suggested to have an impact on the regulation of energy balance.[72] The suggested appetite dysregulation in AN may contribute to the pathophysiology and could be a potential neurobiological treatment target for AN.[70] In a small pilot study ghrelin infusions was administrated to five patients with AN for 14 days with positive results of increase in hunger, nutritional intake and weight gain. The results need to be replicated with a larger sample size and a randomized setting.[73] A RCT from 2018 investigating a ghrelin agonist in outpatient women with AN is included in this systematic review.[66]

1.2.3 Cannabinoids

Dronabinol

The endocannabinoid system has an important role in energy homeostasis and contributes to both appetite and peripheral fat metabolism. Dronabinol is a synthetic cannabinoid receptor 1 (CB1) agonist.[15] Several studies that have investigated the effect of the CB1 agonist on weight gain in different populations (for example cancer-associated anorexia and AIDS-induced anorexia) has reported promising results.[15,74-75] Both the orexigenic and the anabolic effects of dronabinol in other populations inspired some researchers to hypothesize that it might have a positive effect on weight, attitudinal and behavioral dimensions in AN. The RCT from 2013 conducted by these researchers is included in this systematic review.[15]

1.2.4 Other agents

Omega-3 fatty acids

The long hydro-carbon chains containing Omega-3 polysaturated fatty acids (PUFAs) are essential components of the phospholipids in human cells with a positive effect on brain structure and function.[76-77] It has antidepressant effects and diverse results in treatment of anxiety.[78-79] In contradiction to SSRIs efficacy Omega-3 PUFAs is unrelated to nutritional status.[78] Omega-3 PUFAs cannot be produced endogenously though so it has to be consumed by food intake (marine oils).[80] Omega-3 PUFAs influence the gut-brain axis which has been suggested to be involved in AN pathophysiology.[25-27,81] Low Omega-3 PUFA levels and disturbed microbiome diversity has been found in AN.[82-83]

D-Cycloserine

D-Cycloserine is an NMDA-receptor agonist known to facilitate exposure therapy (a therapy method to conquer fears through enhanced learning) and behavioral learning. The drug increases the efficacy of fear extirpation through augmenting glutamatergic function. If D-Cycloserine in combination with exposure therapy can reduce mealtime anxiety and thereby augment weight gain in AN this would be beneficial. Lower weight during treatment is related to higher relapse rates and a high BMI (body mass index) is the best predictor of weight after treatment.[84]

1.2.5 Benzodiazepines

Alprazolam

Alprazolam is a short-acting anxiolytic benzodiazepine that is used as symptomatic treatment. It has a high affinity for the combining site for benzodiazepine in the brain. Except for the anxiolytic effects it has sedative, hypnotic, muscle weakness and anti-convulsive characteristics.[85] Some researchers hypothesized that it would reduce pre-meal anxiety and

thereby lead to an increased caloric intake.[86] The drug is associated with an increased risk of abuse and addiction.[85]

1.3 Other research

There is no recent systematic review with the same methodology and aim as this. There are only two systematic reviews regarding pharmacological treatment of AN recently published.

One is an "umbrella review" from 2019 investigating other systematic reviews and meta-analysis, not only original articles, which is another methodologic approach than mine and also this review does not include all kinds of pharmacological treatment.[87] Neither did they include articles from the databases Embase and PsycINFO and they only included articles until January 2019 so a large multisite study by Attia et al.[88] of olanzapine was not included.

The other one is a systematic review from 2020 investigating pharmacological treatment of just acute-phase AN and not all phases of AN.[43] Neither this included Attia's large multicenter study of olanzapine (because they only included original articles until April 2019).[88] It is also limited to psychopharmacological treatment so all types of medication were not included (for example not ghrelin, oxytocin, omega-3 and dronabinol etc.).

1.4 Aim

To investigate potential pharmacological treatment options of the core symptoms of anorexia nervosa (AN) regarding effectiveness and safety by conducting a systematic review to evaluate the results of quantitative studies (CCTs and RCTs). This systematic review is sought to be useful for clinicals as a gathered picture of the latest research of potential pharmacological treatment of AN and to researchers for future work.

1.5 Questions

Is there any pharmacological treatment of the core symptoms of anorexia nervosa that is effective and safe?

2. METHODS

The methodological approach, a systematic review, was chosen because this research design would best be able to answer my question and present a width of potential pharmacological treatment options. Also, this is a prerequisite to assess the quality and risk of bias of the included studies in a systematic way to better evaluate the results.[89] Since the studies included had high heterogeneity of the study design, populations, interventions, outcome measurements, context etc. it was not possible to perform a meta-analysis which requires homogeneity of the included studies.[90]

2.1 Literature search

Published articles regarding pharmacological treatment of anorexia nervosa were searched for in the online databases PubMed, Embase and PsycINFO. Search criteria (inclusion- and exclusion criteria) were set based upon the purpose and in accordance with recommendations from Forsberg et al.[89] Database specific terms appropriate for each of the databases and Boolean operations were used. The searches were performed in blocks and the search strings for each database could be found in table 1. A limitation of articles from the latest 10 years was chosen in an attempt to just include recent research. Even if the latest 5 years would have been preferable according to Forsberg et al., the latest 10 years (2011.01.01-2021.02.01) was chosen as a compromise based on the limited research in the field.[89] Only quantitative studies with the highly ranked study design RCT and high-quality CCTs were included to minimize bias, in accordance with Forsberg et al.[89] In total 94 articles were found in the three databases

and additional two articles were found by pearl growing. A few conference abstracts were found[33, 90] but the whole grey literature area including manuscripts etc was not covered due to time limitations. Some studies were unavailable in full-text and efforts to find these were not always successful.

2.2 Data analysis

After the literature search was finalized the 96 articles were imported into Covidence.org, an online tool for systematic reviews, for further screening. First a "Title and abstract" screening was initiated to select the articles that best answered my question and fulfilled inclusion and exclusion criteria based upon the PICO strategy (for more details please see table 2).[91] Two reviewers screened, selected and performed a quality assessment independent of each other. In cases of different opinions, the two reviewers discussed and found consensus. If needed a third reviewer was consulted to reach consensus. After abstract screening was completed a full text screening of 23 articles was performed.

12 studies that fulfilled the inclusion- and exclusion criteria were extracted for further quality analyzes according to The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Studies were graded into a quality level ranging from high to very low due to the methodological quality. As all included studies were RCTs, all studies had a high level of evidence at baseline. If bias in some domain was found, the level of quality was downgraded. The grading was performed to evaluate the strength of the scientific material and to be able to make recommendations of different strengths.[89] Quality analysis were based on the outcome measurement that there was found significant evidence for and were not performed for every outcome measurements of the included studies though many of them were not relevant for this systematic review.

A template "Mall för kvalitetsgranskning av randomiserade studier" for quality assessment of randomized studies from SBU was used to perform a systematic evaluation.[92] A minimum level of quality was not required for the articles to be included due to the well-known challenge to recruit anorectics to trials with weight gain as a purpose and issues with low compliance and high drop-out rates which lower the grading of the studies.[38] There are not enough large studies with low drop-out rates to be able to just include studies graded with high quality. If only studies with high quality would have been included the material of this systematic review would have been too narrow and important potential pharmacological treatment options of AN would have been omitted. For the same reason the inclusion limit for drop-out rates that according to SBU should be maximum 30% could not be applied.[92] One of the articles failed to be included due to very low sample size in combination with high drop-out rate (only 10 participants completed the study).[93] Finally, 12 articles were qualified to be included in this systematic review and all of them were RCTs. For further details, A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart could be found in figure 2.

Body mass index (BMI) and weight were chosen to be my primary outcome measurements because they are an important goal of treatment in AN and have a close link to the core symptoms and outcomes.[16, 94] Kaplan et al. found that a high BMI and the rate of weight change was the best predictors of weight maintenance.[94] Weight/BMI is also the most common outcome measurements for this kind of studies and is valid and reliable measurements. When the weight is restored the other core symptoms of AN often normalize. Caloric intake was also chosen as my primary outcome due to the importance of nutritional status and its essential basis for weight regain and recovery. It's also an objective reliable measurement if measured in a reliable way. The secondary measurements of eating disorder psychopathology were chosen to be secondary because many of the studies do not use it as a

primary outcome measurement and this measurement is often more sensitive to bias. To evaluate the safety of the pharmacological treatment side effects and adverse events were also considered.

3. ETHICAL ASPECTS

An ethical approval from an independent Ethical Committee and a written consent from study participants was not relevant for this thesis since it is a systematic review of already published studies and not a clinical trial. Ethical aspects have been carefully considered all along the work. Each included study has been approved by an independent Ethical Committee and states a written consent from each participant. All studies have been conducted in accordance with the Helsinki Declaration of 1975 (revised in 2008) and the participants autonomy in the clinical trials has been considered.[89]

If some ethical concerns of any of the included studies appeared, that study's eligibility was considered. This also accounts for if some of the studies failed to systematically report side effects and adverse events. All included studies except for one (study 4)[2] have proved that they accomplished this. The study of exception probably did measure it even if they didn't report it because they mention that the dose of the intervention was chosen with consideration of knowledge of well-tolerated dose vs efficacy from earlier research and the study was approved by an independent Ethical Committee. Since it's not obvious that they didn't measure side effects and adverse events we chose not to exclude this article. All articles were selected objectively, independently of their results, in accordance with ethical aspects according to Forsberg et al.[89]

This review could guide other researchers in the right direction regarding which interventions could be beneficial to investigate further. Hopefully replication of unnecessary trials (both for

the participants sake and also from a health economical point of view) could be avoided. This could for example be interventions that did not indicate any benefit for the patient (even though the study design was appropriate and the study quality sufficient). Also, other researchers could be motivated to try to replicate the results of promising pilot studies and thereby increase the chances to find effective medications that can improve AN patient's health, quality of life and length of life.

4. RESULTS

The level of evidence of the included studies ranged from high to very low. Even though all studies were RCTs, with a few exceptions the study quality was generally low. In summary, two articles were of high quality, two of moderate quality, four of low quality and four of very low quality (table 4). The weighted quality of all articles was assessed to very low according to GRADE (table 4). For more detailed information regarding the results of the quality assessment please see attachment 1 and table 6. For further details regarding the studies, please see table 3-5.

The overall low quality of the studies was mostly due to the well-known low sample sizes, low compliance and high drop-out rates in this population.[38] Some of the included studies managed to present significant positive results in favor of the intervention despite few observations which indicate that the results probably would have been stronger if the sample size would have been larger. According to Forsberg et al.[89] results from small studies need to be replicated.

4.1 Atypical antipsychotics

The studies included in this systematic review regarding antipsychotics did not evaluate the long-term effects and there is no long-term study recently published.

4.1.1 Olanzapine

The three studies that investigated the atypical antipsychotic dopamine antagonist presented diverse results both regarding my outcome measurements and safety assessment. For more details regarding the studies, please see table 3-5, and for details regarding the quality assessment please see attachment 1 and table 6.

The smallest study conducted 2011 (study 7) by Kafantaris et al.[95] was a pilot study of 10 weeks that investigated olanzapine as adjuvant treatment of adolescents with AN-R. The participants were in-, day- and outpatients. It failed to discover any significant differences between the intervention group and the placebo group in any outcome measurement.[95] This might be due to small sample size (N=20) and high drop-out rate (only 15 participants continued participation during the whole study period of 10 weeks).

Another small pilot study from 2011 (study 8) by Attia et al.[50] investigated 8 weeks olanzapine treatment. The population was outpatient participants over 16 years without other treatment except for SSRIs. The authors presented a significant greater end-of-treatment BMI in the olanzapine group compared to the placebo group ($F(1,20)=6.64$, $p=0.018$) but no significant differences in psychopathology between the olanzapine and placebo group.[50]

A larger multisite study from 2019 (study 1) with the same author as study 8, Attia et al.[88], with an intervention time of 16 weeks investigated adult AN outpatients not in active treatment of any other kind except for other psychotropic medications. This study managed to present a significantly greater increase in BMI of olanzapine (0.259 ± 0.051 versus $0.095 \pm$

0.053 kg/m^2 per month, respectively) compared to placebo but no significant improvement in psychopathological features. Contrary, the ED shape concerns subscale showed significantly greater increase rate in the olanzapine group (0.083 ± 0.049 per month) compared to the placebo group (−0.105 ± 0.053 per month; $F_{1,91}$=7.10, p=0.01).[88]

All three studies had a systematic approach of investigating potential side effects and adverse events. No adverse metabolic effects were noted in study 8 but this study had a small sample size (N=23), a high drop-out rate (26%) and short intervention time of 8 weeks which might have contributed to not being able to establish side effects. The authors pointed out that this might be the case or that anorectics is not affected so severely. Even though study 7 was even smaller (N=20) they found significant elevated glucose levels (-2.02, p=0.05) and insulin levels (t = -2.73, p=0.009) at week 10 in the olanzapine group compared with the placebo group at week 10 (t = -2.44, p=0.02). Study 1 with a higher sample size (N=152) found no significant differences between the two groups regarding metabolic abnormalities though there were side effects in the olanzapine group like concentration issues, restlessness, sleep problems that were significant compared to placebo. The author of this study suggested that olanzapine should be considered as add-on therapy and not as mono-therapy.

Both study 1 and 8 were assessed to have low quality according to GRADE (table 4) due to the high drop-out rates and possible conflict of interest. Except for those risks of biases all other domains were graded to have high quality and a low risk of bias. Study 1 had a very high drop-out rate of 45%. To the study's advantage they managed to report significant results despite the high drop-out rates (it's possible that an even greater effect size than 0.629 would have been evident if lower drop-out rates) and it is a multicenter study with relatively large sample size. Also, a power analysis was conducted and 160 patients were needed to detect a 0.57 lb/week difference between the intervention group and the control group. Study 7 was

graded to a very low quality according to GRADE (table 4) for the same reasons as study 1 and 8 in addition to moderate risk of treatment bias due to compliance issues and diverse co-interventions. For more details regarding the quality assessment please see attachment 1 and table 6. The results of the three studies should be considered preliminary and need to be replicated. Differences in the set-up, co-interventions and population characteristics might have contributed to the different outcomes.

4.1.2 Risperidone

A pilot study (study 6) by Hagman et al.[56] from 2011 investigated adolescent and young adult females with AN in active treatment at different levels (N=40). For more details, please see table 3-5. It reported no significant difference in advantage of risperidone compared to placebo in weight gain, body metabolism or ED (eating disorder) psychopathology except for a significant decrease in the EDI-2 DT subscale by 7 weeks control (effect size: 0.88, p=0.002) but this difference was not maintained by week 11. The authors mentioned that they did not know if the participants that received risperidone did get increased appetite that they struggled against. Risperidone led to elevated prolactin levels but except for that it was well tolerated and no other significant metabolic effects or extra pyramidal symptoms was found.

A power analysis demonstrated that 25 participants were needed to achieve a power of 80% to detect an effect size of 0.81. Only three participants dropped-out from the study and 38 patients participated to the end of the trial which means the study was well-powered. The quality of this article was graded to be high according to GRADE (table 4) with a low risk of bias in all domains. For more details regarding the quality assessment please see attachment 1 and table 6.

4.2 Cannabinoids

4.2.1 Dronabinol

A study from 2013 by Andries et al.[15] (study 5) investigated dronabinol treatment in adults with severe enduring AN. Both in- and outpatients were included (N=25). For more details, please see table 3-5. The authors of this study suggested that an add-on synthetic cannabinoid agonist (dronabinol) might enhance body weight and improve ED-related psychopathological personality traits and behavioral issues in women with advanced AN. The participants that received dronabinol gained 0.66 kg more than placebo (p=0.03) in a 4 weeks period. Any benefit from dronabinol in EDI-2 score changes could not be established. The drug was well tolerated and no serious adverse events were reported.

The short duration and small sample size of the study was a limitation but all but one participant completed the study and a power analyze was performed (16 patients needed to detect a weight gain of 0.5 kg).[15] The quality of the study according to GRADE was graded high (table 4) with a low risk of bias in all domains. For more details regarding the quality assessment please see attachment 1 and table 6. The results seem promising but need to be replicated.

4.3 Hormones

4.3.1 Dehydroepiandrosterone (DHEA)

A pilot study from 2012 by Bloch et al.[61] (study 9) investigated DHEAs effect on 17-47 years old AN outpatients (N=26). The authors hypothesized that DHEA's anabolic and mood stabilizing effects could be beneficial in AN. For more details, please see table 3-5. Their primary outcome measurements were weight and bone mineralization and the secondary were primary anorexic symptoms and mood. This study provided some positive results of BMI

increase in the DHEA group after 4 months of treatment (8.9% compared to baseline) significantly higher than placebo group (Z=-2.0, P=0.05) but these results did not sustain at the time of 6 months of treatment. The BMI increase was positively correlated with improvement in mood exclusively in the DHEA group.[61] DHEA was well tolerated without any adverse events reported. The quality was assessed to very low according to GRADE (table 4). For more details regarding the quality assessment please see attachment 1 and table 6. The results should be considered preliminary and need to be replicated. A larger sample size and a longer treatment period might help to achieve more convincing results.

4.3.2 Oxytocin

Intranasal oxytocin (IN-OT) in the treatment of inpatient women 16 years and older with AN was tested in a RCT study (study 2) by Russell et al.[58], (N=41). For more details, please see table 3-5. There was a significant lower eating concern symptomatology, measured by EDE Eating Concern subscale, 4-6 weeks of oxytocin administration compared to placebo (F(1, 31)=8.934, P=0.006, observed power using alpha (0.05)=0.92, effect size (Eta^2)=0.243). The reduced eating concern is thought to enhance nutritional rehabilitation in AN. Some of the included patients had a BMI higher than 17.5 but sensitivity analysis was performed and these showed that the results above remained significant even if these patients were excluded. IN-OT was well-tolerated and no adverse experiences were found. The same researchers are now conducting a larger multisite study to confirm the results. The authors also suggested more sensitive subjective measurements, longer follow-up and measurement of anxiety outside the hospital setting and if possible, without confounding factors like psychotropic medications. This study was graded as moderate quality according to GRADE (table 4) and even though the results seem promising it should be replicated to draw firm conclusions. For more details regarding the quality assessment please see attachment 1 and table 6.

Another study with within-subject cross-over design conducted by Kim et al.[96] (study 12) from 2015 compared the effect of a single dose oxytocin vs placebo on food intake and emotion recognition in adolescent inpatients with AN, outpatient with BN (bulimia nervosa) and healthy controls. They found no significant effect of oxytocin in either outcome in the AN group (N=35). For more details, please see table 3-5. Adverse symptoms were documented but these results could not be found presented in the article. Different methodological flaws led to high risk of bias and the study was valued to have very low quality according to GRADE (table 4). For more details regarding the quality assessment please see attachment 1. Due to the small sample size and very low quality of the study the results need to be considered preliminary even though it was sufficiently powered according to a power-analysis. A larger sample size, more observations, a less sensitive outcome measurement, more advanced technology and less confounders would be preferable in future studies.

4.4 Benzodiazepines

4.4.1 Alprazolam

A small cross-over study from 2014 (N=17), by Steinglass et al.[86] (study 10) investigated the effects of a single dose alprazolam in adult inpatients with AN. The aim of the study was to investigate if the short-acting benzodiazepine alprazolam could reduce pre-meal anxiety and lead to a greater caloric intake. For more details, please see table 3-5. No increased mean caloric intake or reduced anxiety in the alprazolam group compared to placebo group and no difference between AN-subtypes was found. A side effect of fatigue marginally significantly increased (W=54.5, p=0.08) in the alprazolam group compared to placebo was noted. The authors discuss if the dose was too low to be effective since the failure to achieve reduced anxiety in AN was inconsistent with other research in other subpopulations. The study was

not sufficiently powered after drop-outs and the small sample size could be another reason that no significant results could be presented.

This study was assessed to low quality according to GRADE due to moderate risk of bias due to a moderate drop-out rate of 15%. For further details regarding the quality assessment please see attachment 1. The results were inconsistent with earlier studies in other subpopulations and should be considered preliminary.

4.5 Other agents

4.5.1 Omega-3 fatty acids

A study from 2018 conducted by Brittny et al.[79] (study 11) investigated if omega-3 fatty acids supplementation could be beneficial in anxiety, weight, eating disorder symptoms and depression in adolescent women (N=24) with restrictive AN in a partial hospitalization program. For more details, please see table 3-5. The researchers did not manage to show any positive significant results for the omega-3 group. The omega-3 supplementation was well tolerated with low side effect scores. A power analysis was performed but the study must be considered underpowered. The quality assessment valued the study quality very low according to GRADE (table 4) and the results should be considered preliminary. For further details regarding the quality assessment please see attachment 1.

4.5.2 D-Cycloserine

In a pilot study from 2015 by Cheri at al.[2] (study 4) investigated if D-Cycloserine could improve weight gain by facilitation of exposure therapy in AN patients (N=36) aged 14-49 years old in a partial hospitalization setting. For further details, please see table 3-5. The authors hypothesized that D-Cycloserine facilitation would reduce anxiety during exposure

therapy and accomplish greater weight gain compared to placebo. Body mass index (BMI) was the primary outcome measurement and the study presented significant results in favor of the D-Cycloserine group that accomplished an increase in BMI of 0.385 points compared to 0.098 points in average in the placebo group after four exposure sessions. At 1 month follow-up the D-Cycloserine group continued to increase their BMI in contrast to the placebo group who started to decrease their BMI. The BMI effects were valid even when BMI respectively age was included as a covariant and when adolescents were excluded from the analysis. Anxiety levels significantly decreased over time in both groups. Side effects and adverse events were left out to be reported by the authors.

The quality analysis graded this study to low quality according to GRADE due to high risk of bias mostly because of a high drop-out rate and uncertainty regarding if side effects were measured. A non-significant difference at baseline between the intervention and placebo group might have affected the outcome. For more details regarding the quality assessment please see attachment 1. The results should be considered preliminary and need to be replicated with a larger sample size.

4.5.3 Ghrelin agonist

In a study from 2018 Fazeli et al.[66] (study 3) evaluated the effects of a ghrelin agonist (relamorelin) on weight and gastric emptying in a 4-week trial of outpatient women with AN (N=22). For further details, please see table 3-5. The main findings of the study were a slight trend towards weight gain in the relamorelin group (0.86 ± 0.4 kg) compared to placebo (0.04 ± 0.28 kg; p=0.07) and a significantly shorter gastric emptying time was found in the relamorelin group. In this short period of time relamorelin was well tolerated but long-term studies are needed to evaluate potential side effects in the long run.

The study was graded to have low quality according to GRADE due to a moderate drop-out rate, treatment bias and potential conflict of interests. For further details regarding the quality assessment please see attachment 1. The results should be considered preliminary and future high-quality studies of larger sample size are needed to state if a ghrelin agonist could be beneficial for AN patients.

5. DISCUSSION

Some of the included studies managed to present positive results of my primary outcome measurements in terms of weight gain or BMI increase including, dronabinol, olanzapine (two of the three studies), D-Cycloserine as a facilitator of exposure therapy and partly DHEA (by 4 months but at 6 months). Only one study presented positive effects of my secondary outcome measurement ED psychopathology and that is oxytocin (one of the two studies).

A trend towards significant results regarding weight increase for a ghrelin agonist was also seen. DHEA showed partly significant results in mood improvement at 4 months but not at 6 months. For Risperidone a lower EDI-2DT score by week 7 (but not at week 10) was seen. One possible explanation for this I think might be compliance impairment in the latest part of the trials which is common.[38] Even a modest effect could actually make a difference in the acute phase of AN or in "therapy resistant" patients and of quality of life and should not be underestimated.

An interesting aspect regarding the atypical antipsychotics is that in AN population the weight increase effect seems to be smaller than in other populations according to Attia et al.[88] According to the systematic review from 2012 by Kishi et al.[97], anorectics do not benefit from antipsychotics. Another newer systematic review from 2021 by Márquez et al.[98] found just

one study that presented significant weight gain for Olanzapine compared to placebo. The results regarding psychopathology were contradictory.

Our results are in line with a newly published systematic review regarding treatment interventions for severe and enduring eating disorders from 2020 by Kotilahti et al.[99] that suggests that drug therapies should be considered partly beneficial, especially as add-on therapies. Due to the small effect size of the included interventions, they should probably be considered as an add-on therapy. If there are negative side-effects on health in the long run, some interventions should probably be considered only in the acute phase and maybe for patients that are "therapy resistant". Most of the interventions of the included trials are pilot studies which means there is often no previous research to compare with and most of them have not yet been included in any systematic review to compare with.

A reflection of mine is that one reason why ED-scores were not significantly decreased when weight gain was achieved could be that the weight gain could be contra-productive and often results in increased anxiety and possibly also increased ED-related concerns like body dissatisfaction and eating concerns.

A strength of this systematic review is that it presents a broad perspective. It includes all kinds of pharmacological treatment unlike most previous systematic reviews that often has a focus on only atypical antipsychotics and SSRIs. It also includes the whole AN population (all subtypes, all phases of AN, all ages and gender). Another strength is that it only contains randomized clinical trials which is the strongest and most preferable research design when conducting a systematic review of this kind. The systematic approach which makes the results more reliable is another strength of this review.[89] Also, the search in three databases increased the chances of including a broader material of studies.

Several limitations of this systematic review need to be considered. The high level of heterogeneity of the included studies makes the results hard to compare and the indirectness of evidence low. The included studies applied different diagnostic criteria due to different trial years (DSM-IV/DSM-IV-TR/DSM-V). Population heterogeneity was also high though many of them had a selective population (different subtypes, in-, day- or outpatients, duration of illness, different ages, only women and so on). Different confounding factors like co-morbidity and co-interventions of the study participants is another example. Furthermore, different outcome measurements in the included studies also contributed to the diversity. The studies pharmacological treatment interventions were also different from each other and some studies investigated the intervention as add-on therapy and some as monotherapy. Optimal would have been to have a more homogenous
group to compare but since there is a limited number of RCTs in this research field that was not possible and the broadness of this study would have been hard to accomplish. My selected population reflects the heterogeneity of anorectics.

This systematic review did not include pharmacological treatment of comorbidity (to limit the research) and grey literature was not completely covered. The well-known challenges to recruit and high drop-out rates in this population makes the quality of most of the trials in this population low (table 4, attachment 1).[37-38] Due to this, in addition to the limited selection of RCTs in this field it was not possible to exclude studies of low quality since the number of articles would then have been too small.

I guess that the above-mentioned problems in this population could contribute to the fact that many researchers focus on short term effects instead of long-term effects in their studies. To be considered is the drugs long-term effects on the metabolism, HPA-axel, elevated glucose levels etc. which is considered to have a negative effect on the body and a risk factor of

diabetes type II and cardiovascular diseases and the risk of addiction in benzodiazepines and cannabinoids.[99] Therefore, long-term studies are needed as well as risk benefit analysis. In reality, long-term studies are a challenge to conduct due to the treatment resistance and ambivalence in wanting to get better that we often see in AN.[32,37]

Furthermore, different doses of the interventions should be tested in order to try to establish the optimal dose and to state if there is a dose-response relationship. It's possible that different subtypes of AN react differently at different pharmacological treatments and that the patient's weight and duration of illness could affect the outcome so I think subgroup analysis should be considered to establish if the results are generalizable or apply only to some subgroup. A meta-analysis from 2018 points out the importance of differentiating adolescents and adults regarding psychotherapeutic treatment to optimize the treatment.[100] This I think might also apply for pharmacological treatment.

New potential pharmacological treatment interventions will hopefully be investigated in the future. Psilocybin is one therapeutic drug that has been currently investigated in AN and is suggested to affect cognition and bodily self-perception.[47, 101] Another potential intervention that will be interesting to see if it could be useful in the treatment of AN is estrogen-progestin with an ongoing RCT at the moment.[32]

Future studies should also focus on clarifying the mechanisms of action of treatments to be able to develop new potential medications as well as other treatment options supported by the latest research on the pathophysiology. Other critical aspects of future research are that it should be well-powered and accomplish high methodological quality and to take confounding factors into account. In addition, the study designs of different research groups should be comparable to be able to conduct a meta-analysis. It will be interesting to see what the future

holds. With hopes of progress and new effective treatment options and pharmacological advances.

5.1 Conclusions

In accordance with earlier reviews, we could conclude that there were various levels of evidence from different RCTs regarding the efficacy of pharmacological treatment interventions of the core symptoms of AN. Many of the studies were small pilot studies with small sample size, high drop-out rates and high risk of bias. This is a common problem in drug trials in AN. According to Forsberg et al. results from small studies needs to be replicated.[89] The weighted quality was assessed to very low which means that the results need to be considered preliminary (table 4). Even though some potential drug therapies seemed promising as adjuvant treatment, indicated a positive effect on weight gain/BMI increase or ED pathophysiology in AN (dronabinol, olanzapine, D-Cycloserine as a facilitator of exposure therapy and oxytocin) larger studies are needed to replicate the results in order to establish the potential benefits. All the interventions were assessed to be safe and well tolerated but long-term studies are needed to verify this. Furthermore, the indirectness of evidence made the studies hard to compare since they included different subpopulations of AN and different pharmacological treatment interventions.

In summary, future research should focus on larger high-quality long-term randomized controlled multisite trials, to establish long term benefits and side effects.

6. AUTHORS CONTRIBUTIONS

My contribution to this systematic review reaches from the establishment of research questions to writing the content. It included exploration of the research field, finalizing a project plan, decide inclusion- and exclusion criteria and outcome measurements, collect data, decide search strings, search in databases, find a template for quality assessment, find tools like Covidence and EndNote, decisions to use the PICO strategy and GRADE as a quality assessment tool and perform the quality assessment. The only part that I did not contribute to was the screening and quality assessment by the second reviewer since at least two independent reviewers are needed to conduct a systematic review.

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TABLES

Table 1: Search strings in different databases

Database Search no.	Search terms Date of search	Other inclusion- and exclusion criteria	Results
PubMed	**2021.02.01**		
#1	((Anorexia Nervosa[MeSH Terms]) OR ("anorexia nervosa"[Title/Abstract]))		2 204 763
#2	((((((((((Pharmaceutical Preparations[MeSH Terms]) OR (drug therapy[MeSH Terms])) OR ("pharmacological treatment"[Title/Abstract])) OR ("medical therapies"[Title/Abstract])) OR ("medical therapy"[Title/Abstract])) OR ("drug therapy"[Title/Abstract])) OR ("drug therapies"[Title/Abstract])) OR ("pharmaceutical preparations"[Title/Abstract])) OR ("pharmacological therapy"[Title/Abstract])) OR ("pharmacological therapies"[Title/Abstract])) OR (pharmacotherapy[Title/Abstract])) OR (pharmacotherapies[Title/Abstract])) OR (medications[Title/Abstract])		16 906
#3	#1 AND #2	RCT or CCT, latest 10 years, humans.	**23**
Embase	**2021.02.01**		
#1	'anorexia nervosa'/exp AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [2011-2021]/py		301
#2	'anorexia nervosa':ti,ab,kw AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [2011-2021]/py		284
#3	#1 OR #2		319
#4	'drug therapy'/exp AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [2011-2021]/py		192 812
#5	('drug therapy':ti,ab,kw OR 'drug therapies':ti,ab,kw OR 'pharmacological treatment':ti,ab,kw OR 'medical therapies':ti,ab,kw OR 'medical therapy':ti,ab,kw OR 'pharmaceutical preparations':ti,ab,kw OR 'pharmacological therapy':ti,ab,kw OR 'pharmacological therapies':ti,ab,kw OR pharmacotherapy:ti,ab,kw OR pharmacotherapies:ti,ab,kw OR medication:ti,ab,kw OR medications:ti,ab,kw) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [2011-2021]/py		40 928
#6	#4 OR #5		213 265
#7	#3 AND #6	"Quick limits": humans	**56**
PsycINFO	**2021.02.01**		
#1	((DE "Anorexia Nervosa") OR "Anorexia Nervosa")	"Advanced search": Humans, clinical trials, 2011-2021, "find any of my search terms"	19 418
#2	((DE "Drug Therapy") OR (DE "Hormone Therapy") OR "Pharmaceutical Preparations" OR "pharmacological treatment" OR "medical therapies" OR "medical therapy" OR "drug therapies" OR "pharmaceutical preparations"	Advanced search: Humans, clinical trials*, 2011-2021,	5161

	OR "pharmacological therapy" OR "pharmacological therapies" OR pharmacotherapy OR pharmacotherapies OR medications)	"find any of my search terms"	
#3	1# AND #2		**15**
	*It was not possible to select only CCTs and RCTs in this database so the selection was performed manually when the abstracts/full text articles were read.		
Summary	PubMed: N = 23 Embase: N = 56 PsycINFO: N = 15		**94**

RCT = randomized controlled trial

CCT = controlled clinical trial

Table 2: Inclusion- and exclusion criteria according to PICO

Inclusion criteria	**Exclusion criteria**
Population*	**P**opulation
Humans Any gender Any age People diagnosed with AN (DSM-5/DSM-4/DSM-4-TR/ICD-10) In-/out-/day patients	Animals
Intervention**	**I**ntervention
Pharmacological treatment of the core symptoms of AN	Pharmacological treatment of just comorbidity/secondary disease/ sequela/complications of AN and not the core symptoms of AN
Control group***	**C**ontrol group
Placebo or within-subject (own control) or Treatment as usual (TAU) or other treatment	
Outcome	**O**utcome
<u>Primary outcome measurements:</u> BMI/Weight/Caloric intake <u>Secondary outcome measurement:</u> Eating-disorder psychopathology Including at least one of the primary or secondary outcome measurements	None of the outcome measurements: BMI/Weight/ Caloric intake Eating-disorder psychopathology
Other criteria: Original article: RCT or CCT Publication date: latest 10 years (2011.01.01-2021.02.01) All languages	**Other criteria:** Systematic review or metanalysis

*Both subtypes (AN-R and AN-BP) and all ages were included to address the whole population of people with AN, even though many of the included articles include only a limited sub- and/or age group. Also, it would have been too few articles to present if only a selected group of AN would have been chosen. Minimum sample size was not set as an inclusion criterion, instead this was evaluated from case to case based upon power analysis and drop-out rate etc.

**No time, dose or intensity preferences was specified as inclusion criteria since different interventions require different doses, intensity and time due to different mechanisms of action and pharmacokinetics. To limit the research, this systematic review does not include pharmacological treatment of comorbidity or sequela.

***Optimal would have been to apply the same control settings but of course this is utopia since different clinical trials have different control groups and there are not enough studies to review with the same control group settings.

Table 3: Article matrix 1: Main findings

Study nr. (Ref.)	Author	Title	Year	Study type	Main findings	Quality assessment (GRADE)
1. (#25)	E. Attia et al.[50]	**Olanzapine** versus Placebo in Outpatient Adults with Anorexia Nervosa: A randomized clinical trial	2019	RCT Double blind	A greater increase in **BMI** of olanzapine (0.259 ± 0.051 versus 0.095 ± 0.053 kg/m^2 per month, respectively) compared to placebo group. **Concentration** issues, **restlessness**, **sleep** problems significantly in I vs C.	LOW ⊕⊕⊖⊖
2. (#20)	J. Russel et al.[58]	Intranasal **oxytocin** in the treatment of anorexia nervosa: Randomized controlled trial during re-feeding	2018	RCT Double blind	**EDE Eating Concern** significantly lower in I vs C by 4-6 weeks (F(1, 31)=8.934, P=0.006, observed power using alpha (0.05)=0.92, effect size (Eta^2)=0.243).	MODERATE ⊕⊕⊕⊖
3. (#55)	P. K. Fazeli et al.[66]	Treatment with a **Ghrelin Agonist** in Outpatient Women with Anorexia Nervosa: A Randomized Clinical Trial	2018	RCT Double blind	**A slight trend** towards **weight gain** in I (0.86 ± 0.4 kg) compared to C (0.04 ± 0.28 kg; p=0.07) but when controlling for baseline VAS hunger score the reults were similar. A significantly **shorter gastric emptying time** in I vs C, P=0.03.	LOW ⊕⊕⊖⊖
4. (#33)	C. A. Levinson et al.[2]	**D-Cycloserine** Facilitation of Exposure Therapy Improves Weight Regain in Patients With Anorexia Nervosa: A	2015	RCT Double blind Pilot study	Increase in **BMI** of 0.385 points compared to 0.098 points in average in the placebo group after four exposure sessions. At 1 month follow-up the D-Cycloserine group continued to increase their BMI in contrast to the	LOW ⊕⊕⊖⊖

		Pilot Randomized Controlled Trial			placebo group who started to decrease their BMI.	
5. (#10)	A. Andries et al.[15]	**Dronabinol** in Severe, Enduring Anorexia Nervosa: A Randomized Controlled Trial	2013	RCT Double blind Cross-over design	**Weight** gain in the dronabinol group of 0.66 kg more than placebo (p=0.03) in a 4 weeks period.	HIGH ⊕⊕⊕⊕
6. (#3)	J. Hagman et al.[56]	A double-blind placebo controlled study of **risperidone** for the treatment of adolescents and young adults with anorexia nervosa: a pilot study	2011	RCT Double blind Pilot study	A significant decrease in the **EDI-2 DT subscale** in I compared to C by 7 weeks control (effect size: 0.88, p=0.002) not maintained by week 11 **Elevated prolactin** levels.	HIGH ⊕⊕⊕⊕
7. (#36)	V. Kafantaris et al.[95]	A Placebo-Controlled Pilot Study of Adjunctive **Olanzapine** for Adolescents with Anorexia Nervosa	2011	RCT Double blind Pilot study	**No** significant differences between C and I of any outcome measurements. **Elevated glucose** levels (-2.02, p=0.05) **and insulin** levels (t = -2.73, p=0.009) at week 10 in I vs C at week 10 (t = -2.44, p=0.02).	VERY LOW ⊕⊖⊖⊖
8. (#1)	E. Attia et al.[50]	**Olanzapine** versus placebo for out-patients with anorexia nervosa	2011	RCT Double blind	Significantly higher end-of-treatment **BMI** in the I compared to C (F(1,20)=6.64, p=0.018).	LOW ⊕⊕⊖⊖
9. (#119)	M. Bloch et al.[61]	**Dehydroepian drosterone** treatment effects on weight, bone density, bone metabolism and mood in women suffering from anorexia	2012	RCT Double blind Pilot study	**BMI** increase in the DHEA group after 4 months of treatment (8.9% compared to baseline) significantly higher than placebo group (Z=-2.0, P=0.05) but these results did not sustain at the time of 6 months of treatment. The BMI increase was positively correlated with improvement in mood	VERY LOW ⊕⊖⊖⊖

		nervosa—a pilot study			exclusively in the DHEA group.	
10. (#15)	J. E. Steinglass et al.[86]	The (Lack of) Effect of **Alprazolam** on Eating Behavior in Anorexia Nervosa: A Preliminary Report	2014	RCT Double blind Cross-over design	**No** significantly increase in any outcome measurements. **A Side effect of fatigue** marginally significantly increased (W=54.5, p=0.08) in I.	MODERATE ⊕⊕⊕⊖
11. (#37)	B. E. Manos et al.[79]	A pilot randomized controlled trial of **omega-3** fatty acid supplementation for the treatment of anxiety in adolescents with anorexia nervosa	2018	RCT Double blind Pilot study	**No** significant differences between I and C of any outcome measurements.	VERY LOW ⊕⊖⊖⊖
12. (#16)	Y-R. Kim et al.[96]	The Impact of **Oxytocin** on Food Intake and Emotion Recognition in Patients with Eating Disorders: A Double Blind Single Dose Within-Subject Cross-Over Design	2015	RCT Double blind Cross-over study	**No** significant differences between I and C in any outcome measurements.	VERY LOW ⊕⊖⊖⊖

Table 4: Article matrix 2: PICO information, drop-out rates and co-interventions

Study nr. Ref.	Population (P) (At baseline)	Intervention (I)	Control (C)	Sample size (C=Control, I=Intervention) Drop-out rate (%)	Primary outcome measurements (O)	Secondary outcome measurements (O)	Co-interventions	Certainty of the evidence (GRADE)
1. #25	AN (DSM-IV except for some patients not fulfilling the amenorrhea criteria) Outpatients Age: 18-25 years BMI (kg/m^2): 14-18.5	Olanzapine 2.5 mg - 10 mg/day** 16 weeks	Placebo	152 (I:75, C:77) 45.4%	Weight YBOCS	EDE CES-D Zung Anxiety Inventory CGI	Other psychotropic medications	LOW ⊕⊕⊖⊖
2. #20	AN (DSM-IV) Inpatients Women Age: 16 years or older BMI (kg/m^2): <19.5	Oxytocin 50 µL of OT (9 IU) 4-6 weeks	Placebo	41 (I: 20, C:21) 19.5%	Weight gain Change in: EDE scale Cognitive rigidity Social anxiety Obsessive symptoms Autistic symptoms		Nutritional rehabilitation in a hospital setting	MODERATE ⊕⊕⊕⊖
3. #55	AN (DSM-V) Outpatients Women Mean age: 28.9 +/- 2.4 years BMI (kg/m^2): I:17.6 C: 17.8	Ghrelin agonist 100 mcg subcutaneously daily 4 weeks	Placebo	22 (I:10, C:12) 13.6%	Change in: Weight Gastric emptying time	VAS hunger score Ghrelin levels IGF-1 levels	Long-term outpatient therapy in most of the cases. Other medications were allowed if they were on a stable dose for at least 2 weeks.	LOW ⊕⊕⊖⊖
4. #33	AN (DSM-IV) Partial hospitalization setting Age: 14-49 years Mean BMI (kg/m^2): 20 (15-24)	D-Cycloserine 250 mg before 4 sessions of exposure therapy	Placebo	36 (I:20, C:16) 22.2%	BMI	Process variables: Anxiety % Meal completed	Exposure therapy and structured psychoeducation	LOW ⊕⊕⊖⊖

5. #10	**AN (DSM-IV-TR)** **In- and outpatients** **Age: 18 years or older** **BMI (kg/m^2): not presented in the article**	**Dronabinol 2.5 mg x 2** **4 weeks**	**Placebo**	**24** **4.0%**	**Mean change in body weight**	**EDI-2 scale**	**Standard psychotherapy and nutritional interventions**	HIGH ⊕⊕⊕⊕
6. #3	**AN (DSM-IV)** **In-, day- or outpatients** **Women** **Age: 12-21 years** **Mean BMI (kg/m^2): 16**	**Risperidone 0.5 mg – 4.0 mg***** **Mean duration: 9 weeks**	**Placebo**	**40 (I: 18, C: 22)** **7.3%**	**EDI-2** **BIS**	**BMI** **REE** **MASC** **SAS** **BIS** **CAPT**	**Family centred care, care as usual** **Antidepressants**	HIGH ⊕⊕⊕⊕
7. #36	**AN-R (DSM-IV except for some patients not fulfilling the amenorrhea criteria)** **In-, day- and outpatients** **Age: 12-21 years** **BMI (kg/m^2): 13.4-18.2**	**Olanzapine 2.5 mg - 10 mg/day*** **10 weeks**	**Placebo**	**20 (I:10, C:10)** **25%**	**%MBW**	**Psychological functioning** **Laboratory assessments (including indirect calorimetry)**	**Varying levels of care:** **Day-, in- and outpatient treatment**	VERY LOW ⊕⊖⊖⊖
8. #1	**AN (DSM-IV)** **Outpatients** **Age: 16 years or older** **BMI (kg/m^2): 14-19**	**Olanzapine 2.5 mg - 10 mg/day**** **8 weeks**	**Placebo**	**23 (I:11, C:12)** **26.1%**	**BMI (kg/m^2)**	**YBC-EDS** **BAI** **BDI** **BSQ** **Eating disorder Inventory** **PANSS**	**SSRIs**	LOW ⊕⊕⊖⊖
9. #119	**AN (DSM-IV)** **Outpatients** **Age: 17-47 years** **Mean BMI (kg/m^2): 17.8**	**Dehydroepiandrosterone (DHEA) 100 mg** **6 months**	**Placebo**	**26 (I:15, C:11)** **19.2%**	**BMI (kg/m^2):** **BDI** **EDI, CGI-M** **Bone mineral density and bone metabolism**		**Dynamic psychotherapy and group cognitive/ supportive psychotherapy** **Nutritional assessments**	VERY LOW ⊕⊖⊖⊖
10. #15	**AN (DSM-V)** **Inpatients** **Age: 18-60 years**	**Alprazolam 0.75 mg** **A single dose**	**Placebo**	**17 (I:17, C:17)** **0%**	**Caloric intake**	**Anxiety:** **POMS tension** **STAI-S** **POMS fatigue**	**Inpatient treatment** **Antidepressants**	MODERATE ⊕⊕⊕⊖

	Mean BMI (kg/m^2): 18 (+/- 0.6)							
11. #37	**AN-R (DSM-V)** **Women** **Age: 12-21 years** **Mean BMI (kg/m^2):** **I: 19.6** **C: 18.8**	**Omega-3 PUFA (2,120 mg eicosapentaenoic/600 mg docosahexaenoic acid)** **12 weeks**	**Placebo**	**24 (I:12, C:12)** **25%**	**BAIT**	**BMI** **Medical tolerability** **EAT-26** **CES-D**	**Partial Hospitalization Program (PHP)** **SSRIs**	VERY LOW ⊕⊖⊖⊖
12. #16	**AN (DSM-V)** **Women** **Mean age: 21.97 years** **Mean BMI (kg/m^2): 15.07**	**Oxytocin 35.2 mg** **A single dose**	**Placebo**	**AN: 43 (I:43, C:43)** **18.6%**	**Caloric intake** **Immediate consummatory behaviour of juice intake** **Sensitivity to emotion recognition**		**Inpatient treatment** **Fluoxetine**	VERY LOW ⊕⊖⊖⊖

Weighted quality	**A. Quality assessment of individual studies: -1 (with few exceptions most of the included studies was assessed to low or very low quality)** **B. Heterogeneity: -1 (diverse interventions, settings, populations, co-interventions, outcome measurements etc.)** **C. Indirectness of evidence: -1 (different subgroups: AN-R/AN-BP, add-on-/mono therapy, different phases of AN etc.)** **D. Imprecision: -1 (low sample sizes and high drop-out rates)** **E. Publication bias: -1 (some concerns regarding some studies that were sponsored)** **F. Effect size (not enough to raise the grading)** **G. Dose–response relationship (not enough to raise the grading)**	VERY LOW**** ⊕⊖⊖⊖

*the dose was increased with 2.5 mg every week up to 10 mg if the medication was tolerated by the patient.

**the dose was increased with 2.5 mg every 2 weeks up to 10 mg if the medication was tolerated by the patient.

***the dose was increased with 0.5 mg every week up to maximum 4.0 mg.

****Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect [102]

(AN = Anorexia Nervosa)

(ED = Eating disorder)

(SR = Systematic review)

(RCT = Randomized controlled trial)

(CCT = Controlled clinical trial)

(TAU = Treatment as usual)

Table 5: Article matrix 3: Outcome measurement results and side effects/adverse effects

Study nr. Ref.	Intervention	Outcome measurement BMI kg/m²	Outcome measurement Weight (kg)	Outcome measurement ED-psychopathology	Side-effects/adverse events	Quality assessment (GRADE)
1. #25	**Olanzapine**	A greater increase in **BMI** of olanzapine (0.259 ± 0.051 versus 0.095 ± 0.053 kg/m² per month, respectively) compared to placebo group.	-	-	**Concentration** issues, **restlessness**, **sleep** problems significant in I vs C	LOW ⊕⊕⊖⊖
2. #20	**Intranasal oxytocin**	-	-	**EDE Eating Concern** significantly lower in I vs C by 4-6 weeks (F(1, 31)=8.934, P=0.006, observed power using alpha (0.05)=0.92, effect size (Eta^2)=0.243).	-	MODERATE ⊕⊕⊕⊖
3. #55	**Ghrelin Agonist**	-	**A slight trend** towards **weight gain** in I (0.86 ± 0.4 kg) compared to C (0.04 ± 0.28 kg; p=0.07) but but when controlling for baseline VAS hunger score the reults were similar. A significantly	-	-	LOW ⊕⊕⊖⊖

			shorter gastric emptying time in I vs C, P=0.03.			
4. #33	**D-Cycloserine** Facilitation of Exposure Therapy	Increase in **BMI** of 0.385 points compared to 0.098 points in average in the placebo group after four exposure sessions.	-	-	*Left out to be reported by the authors.*	LOW ⊕⊕⊖⊖
5. #10	**Dronabinol**	-	**Weight** gain in the dronabinol group of 0.66 kg more than placebo (p=0.03) in a 4 weeks period.	-	-	HIGH ⊕⊕⊕⊕
6. #3	**Risperidone**	-	-	A significant decrease in the **EDI-2 DT subscale** in I compared to C by 7 weeks control (effect size: 0.88, p=0.002) not maintained by week 11	**Elevated prolactin** levels	HIGH ⊕⊕⊕⊕
7. #36	**Olanzapine**	-	-	-	**Elevated glucose** levels (-2.02, p=0.05) and insulin levels (t = -2.73, p=0.009) at week 10 in I vs C at week 10 (t = -2.44, p=0.02).	VERY LOW ⊕⊖⊖⊖
8. #1	**Olanzapine**	Significantly higher end-of-treatment **BMI** in the I compared to C (F(1,20)=6.64, p=0.018).	-	-	-	LOW ⊕⊕⊖⊖
9. #119	**Dehydroepiandrosterone (DHEA)**	**BMI** increase in I after 4 months (8.9% compared to baseline) significantly	-	-	-	VERY LOW ⊕⊖⊖⊖

		higher than C (Z=-2.0, P=0.05) but did not sustain at 6 months. The BMI increase positively correlated with improvement in mood only in the DHEA group.				
10. #15	**Alprazolam**	-	-	-	**A Side effect of fatigue** marginally significantly increased in I (W=54.5, p=0.08).	MODERATE ⊕⊕⊕⊖
11. #3	**Omega-3**	-	-	-	-	VERY LOW ⊕⊖⊖⊖
12. #16	**Oxytocin**	-	-	-	-	VERY LOW ⊕⊖⊖⊖

I = Intervention group

C = Control group

Table 6: Risk of bias

Study nr. Ref.	Selection bias	Treatment bias	Assessment bias	Drop-out bias	Reporting bias	Conflict of interest bias	Overall
1. #25	+	+	+	–	+	o	–
2. #20	+	+	+	o	+	+	o
3. #55	+	o	+	o	+	o	–
4. #33	+	+	+	–	o	+	–
5. #10	+	+	+	+	+	+	+
6. #3	+	+	+	+	+	+	+
7. #36	+	o	+	–	+	o	–
8. #1	+	+	+	o	+	o	–
9. #119	+	+	o	–	o	o	–
10. #15	+	+	+	o	+	+	o
11. #37	+	o	+	–	+	o	–
12. #16	+	+	o	–	o	+	–

– = high risk of bias

o = moderate risk of bias

+ = low risk of bias

FIGURES

Figure 1: DSM-V classification according to APA 2013 (remission and severity specifiers not specified)[16]

Anorexia Nervosa

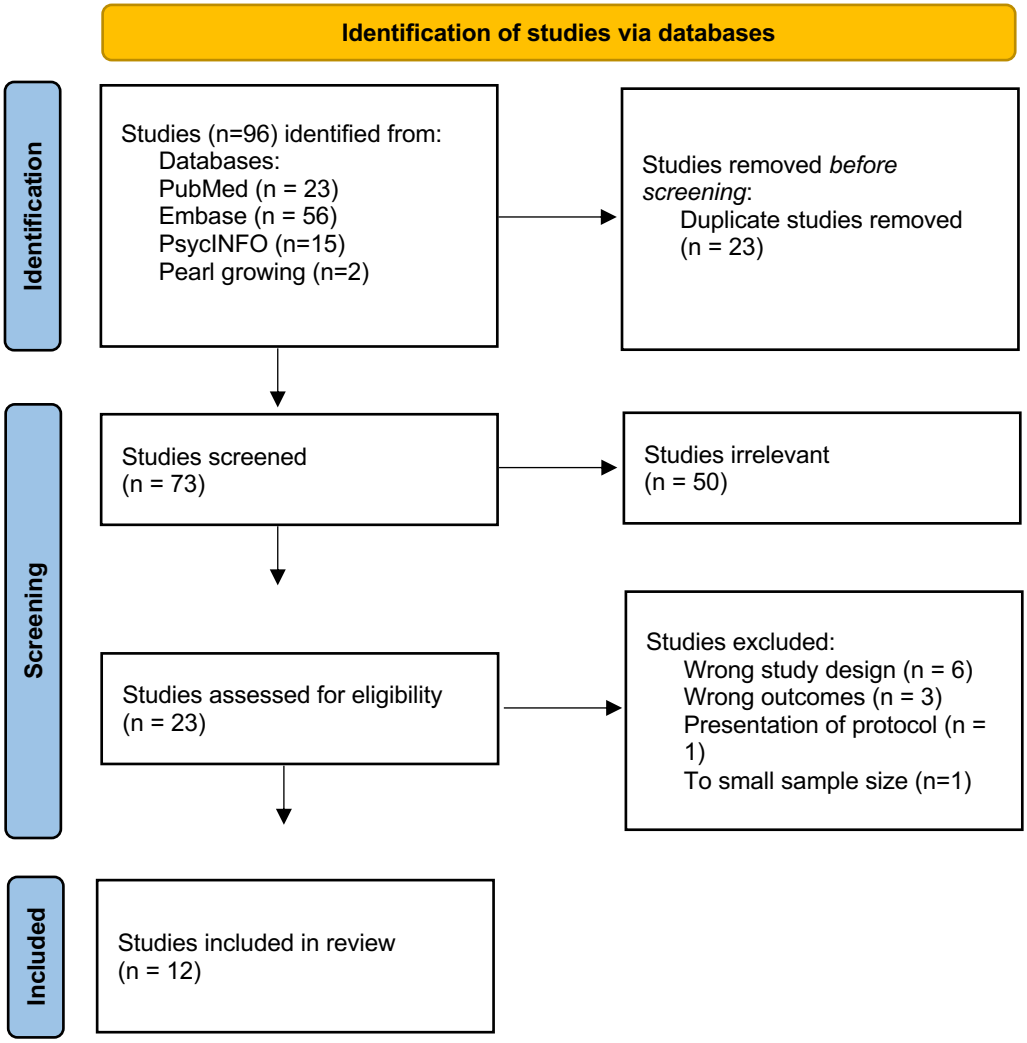
A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify whether:

(F50.01) **Restricting type**: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting and/or excessive exercise.

(F50.02) **Binge-eating/purging type**: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Figure 2: PRISMA flow chart



Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

APPENDIX

Attachment 1: Please see the uploaded file at OneDrive:

"Quality assessment Study 1-12.pdf" (please see "Bilaga 2-Mall för kvalitetsgranskning av randomiserade studier" for each study in the attachment)