A network meta-analysis of anorexia treatments in disease and old age: pharmacogenomics, the gut-brain axis and artificial neural nets. Where are we?

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Abstract

Anorexia affects millions of people worldwide, and treatments vary widely, with no definitive treatment guidelines. A network meta-analysis compared and contrasted existing treatments for chronically ill and elderly patients. EMBASE, MEDLINE, PubMed, Cochrane, and clinicaltrials.gov were searched for articles reporting weight/body mass index changes pre- and post-treatment in the last 65 years. The target population was anorectic adults with chronic long-term illness (cancer, HIV, cystic fibrosis) or the elderly (ages over 65). Outcomes using pooled-weighted-standard-mean effect sizes were analyzed using a random effects model with Bayesian and frequentist methods. Meta-regressions with artificial neural nets were used to validate results and predict response to treatments. A total of 74 studies were included in the network meta-analysis out of the retrieved 340 articles, and 16,390 patients were analyzed in total. The random effects model calculated a pooled-weighted-effect size ($p<0.0001$) for olanzapine [0.87, confidence interval (CI) 95% (0.66-0.97)], for megestrol acetate high-dose [0.72, CI 95% (0.53-0.91)], for anamorelin [0.56, CI 95% (0.36-0.77)], for megestrol acetate low-dose [0.47, CI 95% (0.25-0.69)], for mirtazapine [0.42, CI 95% (0.13-0.72)], and for nutritional supplementation [0.45, CI 95% (0.29-0.61)]. Cannabinoids, cyproheptadine, other antidepressants, and steroids did not perform well. Between-study heterogeneity was tau-squared (τ^2)=0.03. Subgroup analysis indicates that olanzapine is most effective for cancer patients, followed by megestrol acetate in high doses and anamorelin. Results were inconclusive for other patient groups. Olanzapine-induced weight gain is an adverse drug reaction that can be explained by pharmacogenomics affecting gut-microbiota dysbiosis. Compared to megestrol acetate and anamorelin, it has fewer side effects, improves sleep and mood, and has proven anti-nausea/anti-vomiting effects in chemotherapy. Furthermore, it inhibits some types of cancer cells and can be cytotoxic. Drug repositioning of olanzapine and anamorelin for cancer, elderly, HIV, and cystic fibrosis patients as orexigenic agents should be explored further. Appropriate nutritional supplementation should augment anorexia treatments.

Introduction

Chronic diseases such as cancer (CA), cystic fibrosis (CF), AIDS, or chronic obstructive pulmonary disease (COPD) often cause appetite loss, secondary to surgery, chemotherapy, medication, or disease sequelae. As a result, patients may become cachectic

or sarcopenic.[1] It is estimated that anorexia-induced cachexia accounts for over 30% of deaths among CA patients.[2] In 2019, CA caused over 10 million deaths worldwide, with more than 80% of CA patients experiencing anorexia. Notably, 3 million CA deaths were attributed to anorexia and cachexia rather than CA itself.[3,4]

Similarly, appetite loss is estimated in more than 25% of older adults (aged 65 years and over). In patients with chronic kidney disease, CA, chronic pain, or post-gastrointestinal surgery, these percentages are significantly higher and can be up to 59%.[5]

High prevalence of the avoidant restrictive food intake disorder (ARFID) has been reported in older adult populations, which has been linked to fear of choking, gastrointestinal disorders, as well as smell and taste alterations.[6]

Anorexia of aging leads to poor nutritional status, sarcopenia, significant impairment, and sometimes death. Older adults are more likely to suffer from multiple syndromic conditions such as chronic diseases, CA, cognitive impairment, and dementia, which lead to anorexia, weight loss, and frailty. Frailty, a major geriatric syndrome, is a complex multi-factorial process with psycho-social and physical components that has become a major public health concern in the past decade. There are multiple tools that assess frailty in older adults, and although nutrition has been shown to be a very important element, there is not enough emphasis on the assessment of the nutritional phenotype specifically. There is ongoing research on the way the nutritional component of frailty affects the gut microbiome; however, there are limited published data.[7-9]

Although there are no set treatment guidelines for any type of anorexia and nutritional frailty in most countries, many studies report that such patients are treated pharmacologically. Off-label medications used include antipsychotics, antidepressants, antihistamines, synthetic progestins, corticosteroids, and cannabinoids. Such treatments are not specifically approved for anorexia, and their use is based largely on observed side effects rather than established efficacy.[10-13]

The gut-brain axis has been shown to affect the immune system and to play a pivotal role in the orexigenic pathway. Though usually modulated by diet, it can be significantly affected in chronic disease and with age. Physiological changes, medical treatments, chemotherapy, and radiotherapy are some of the reasons microbiota in this axis are expressed or react differently. Emerging research suggests that alterations in gut microbiota in individuals with anorexia affect the pharmacokinetics of oral drugs, with some studies linking these changes to specific genetic loci.[2,14,15] While nutritional support is essential for all anorexia patients, it has limited effectiveness, and appetite or weight improvements are often not sustained.[5,16]

This network meta-analysis (NMA) compares and contrasts some of the main anorexia treatments in chronic illness and old age, such as different types of pharmacotherapies and nutritional supplementation.

Methods

An NMA of anorexia treatments for patients with chronic illness (CA, CF, HIV/AIDS, COPD) and for elderly populations with body mass index (BMI)/weight loss was conducted as per the PRISMA-NMA guidelines.[17] As studies used a variety of measurement scales and tools for treatment efficiency, Hedge's g [standardized mean difference (SMD)] was calculated as the main outcome of treatment success. Primary study outcomes were BMI or weight changes of treated *vs* untreated patients. A significant number of recent studies report that such changes can be pivotal in patient survival.[18]

Databases searched were EMBASE, MEDLINE, Cochrane, PubMed, and clinicaltrials.gov. Search criteria were anorexia treatments in the last 65 years (first search December 15th, 2023, last search December 30th, 2024). Full search arguments can be seen in the *Supplementary Material*.

Study designs for review were randomized controlled trials (RCTs), and real-world evidence (RWE) such as cohort studies, retrospective reviews, register data, and open-label trials published in evidence-based peer-reviewed journals. Incomplete studies were excluded. All authors agreed that RWEs, while traditionally ignored in older types of network meta-analyses, should be included in this NMA. The incorporation of such data is a novel approach for network meta-analyses. Especially in cases where quality RCTs are lacking (*e.g.*, anorexia of old age).[19]

Although such approaches may increase uncertainty in the network initially, individual participant data analysis,[20] hierarchical models with Monte Carlo simulations (MCMC), and sensitivity analyses can mitigate this uncertainty by introducing a posterior distribution with these data. Elastic predictive/power priors were incorporated into the non-RCT part of the network to control and downgrade the contribution of these data and reduce type I and type II errors.[21] Extensive sensitivity analyses were performed to determine the robustness of the data.[19] The dataset was analyzed with three different statistical methods. Detailed study descriptives can be seen in the *Supplementary Material*.

The patient population consisted of adults (older than 18 years old) with a diagnosis of anorexia secondary to chronic illness such as CA, HIV/AIDS, CF, COPD, or elderly patients with chronic illness, with or without dementia (adults over 65 years old).

Treatment interventions were antidepressants, antipsychotics, synthetic hormones, corticosteroids, cannabinoids, antihistamines, or ghrelin agonists, as well as nutritional supplementation.

There were no ethnic, language, or geographical restrictions. The same query terms and inclusion criteria were used across all searched databases.

References were exported and consolidated into a single EndNote library, where duplicates were removed. The studies were then uploaded to Covidence, a web-based platform for collaborative systematic reviews, where they underwent a second screening process. Studies progressed to the data extraction phase if all authors reached consensus. Any disagreements were discussed and resolved through voting. A standardized template was used to extract data, including authorship, publication year, country, study type, patient age and sex, patient population, sample size, control groups, baseline and final patient data, intervention details (type and duration), outcomes, follow-up information, and study limitations. RCTs were included if they incorporated the revised Cochrane risk of bias tool or were assessed by all authors as having low risk of bias. Systematic reviews and meta-analyses were evaluated using the AMSTAR-2 tool. The quality of NMA evidence was assessed with CINeMA, as per the Cochrane handbook.[22,23]

Studies were categorized based on type (RCTs or RWE), type of intervention, lead researcher, year of publication, and patient group. Data were then imported into SPSS v30 (IBM, Armonk, NY, USA) for further analysis. Extensive study details, as well as categorizations, can be seen in the *Supplementary Material*.

For each study included, BMI or weight changes and treatment outcomes, as reported by the original authors, were used to calculate Hedge's g effect sizes for each study. Using individual participant data has been shown to mitigate bias and increase reliability.[20] Control group treatment success and failure rates were used for comparison, and attrition rates were factored into the overall weight calculation for each study. Effect sizes for BMI or weight changes were computed as per Cohen and Hedges.[24,25] Paired sample effect sizes were calculated as per Gibbons *et al.*,[26] with within-sample correlation corrections and meta-analyses as per Borenstein *et al*.[27]

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The sensitivity analyses performed identified a random effects model as the best fitted model, and they were conducted as follows:

i) CiNeMA: a NMA tool that is more comprehensive than GRADE/2 as it addresses additional domains such as within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence;[22]

ii) Bayesian statistics: hierarchical networks with MCMC and the Gibbs sampler, incorporating elastic (power) priors to minimize bias for non-RCTs.[19,28,29] The models ran with 60,000 adaptation iterations and 140,000 simulation iterations. The inference was that all necessary information to determine treatment success or failure was embedded within the data. The hypothesis proposed that patient responses to treatment are driven by adverse drug reactions (ADR), which are influenced by individual genetic variations. SMD and standard errors were used for comparisons between treatments. The surface under the cumulative ranking (SUCRA) scores were used to present the cumulative sum of the vector of probabilities for each treatment rank after the completion of the MCMC cycles.[30] Both fixed-effects and random effects models were tested. The best-fitting model selected based on the lowest deviance information criterion, for lower inconsistency,[31] was the random effects model. Network convergence was evaluated using the potential scale reduction factor, assessed through the Gelman-Rubin diagnostic plots;[32,33]

iii) frequentist methods:[34] this approach assumed no differences between treatments, with the primary outcome being the vector of p-scores derived after appropriate network iterations and adjustments. To minimize bias, models were penalized for between-study variance using the least-squares approximation with $\ell 1$-norm regularization,[35] net heat plots,[36] and the node splitting method,[29] were used to assess inconsistency.

Transitivity and consistency were calculated according to the method of Efthimiou.[37] Between-study heterogeneity was calculated using tau-squared (τ^2).[38] A K-means clustering algorithm (Euclidean distance minimization) was used to identify and classify patterns in treatment efficiency across all included studies.[39] Treatment success was defined according to Cohen and Hedges,[24,25] with bias-corrected SMD. Small effect was 0.20, 0.50 was a moderate effect, and 0.80 was a large effect.

All calculations and network modelling were performed using R version 4.3.3. Custom scripts were developed to automate the entire process, including testing, results, and graph production.

To establish the robustness of conclusions, network meta-regressions were conducted using supervised learning networks, alongside R,[40] using the Bayesian model, as frequentist modeling does not allow for meta-regressions. This allowed us to evaluate the models' ability to predict treatment outcomes and identify any study characteristics that might have influenced results.

A series of feedforward networks with backpropagation algorithms, based on the multilayer perceptron, were used to test the networks' capacity to predict treatment efficiency and to identify statistically significant covariates. Covariates were rescaled and normalized for consistency. The hidden layer activation function used was hyperbolic tangent, the error function was cross-entropy, and the activation functions at the output layer tested were identity and hyperbolic tangent (159-161). Covariates tested were BMI/weight before and during treatment, treatment duration, type of treatment, and mode of action/ADR effects.

Reviewed and included studies, type of study, study characteristics, patients, countries, and risk of bias classifications are detailed in the *Supplementary Material*.

No actual patients were involved in the analysis. All patient data were anonymous and had been previously published in peer-reviewed manuscripts.

Results

In the PRISMA-NMA flowchart in Figure 1, the search strategy and reviewed studies are shown. In Table 1, treatment comparisons, patients, types of studies, intervention, and control groups are summarized per condition. There were 74 studies in total. The non-RCT component was downgraded with elastic power prior = 0.05. Detailed information about each study can be seen in the *Supplementary Material*, pages 8-24.

In Table 2, the network-generated netranking p-scores for each intervention type for the above patient groups can be seen in more detail. The ranking of results was per treatment intervention, based on the R calculations for the NMA. The mean of all 1-p[j]-scores was computed, based on the point estimates and standard errors of the network calculation. Where p[j] symbolizes the one-sided p-value of accepting the H_1 alternative hypothesis that the treatment in question is better compared to the other (j) treatments. This means that if a treatment is worse than others, its p-score is bigger. These p-scores represent the certainty that a treatment is better than another, averaged over all other compared treatments, and are comparable to the SUCRA score, where 1 is best and 0 is worst. Individual risk of bias scores for each study can be seen in the *Supplementary Material*, pages 6-28, in column 6, whilst CiNeMA confidence scores/bias for the entire NMA can be seen in the *Supplementary Material*, pages 34-38. Network estimates and pairwise comparisons can be seen in the *Supplementary Material*, page 30. Network inconsistency can be seen in the netheat plots in the *Supplementary Material*, page 33.

A further subgroup analysis per condition revealed that the below anorexia treatment ranking was relevant to CA patients, and inconclusive for other patient groups, despite being treated with the same drugs.

Figure 2 shows the NMA geometry, per intervention type, for all analysed patients. The network is depicted using two different algorithms. Each sphere represents a treatment intervention. The strength of the network comparisons is the thickness of the lines within the geometric depictions.

In Figure 3, individual studies can be seen, grouped by intervention type, as categorised by the NMA.

Results of each treatment intervention relative to placebo can be seen in the forest plots in Figures 4A and B. Weighted pooled effect sizes per treatment type are presented for all patients, relative to placebo. Olanzapine shows as more effective compared to other interventions. It should be noted that the model penalised interventions, taking into account death rates, attrition rates, duration of treatments, and side effects. It was not possible to reach statistically significant results for other patient groups.

From the subgroup analysis, olanzapine, compared to other treatments, was the most effective treatment for patients, as can be seen in Figures 4C and D.

Additional results for megestrol acetate (MA), mirtazapine, cannabinoids, and anamorelin can be seen in the *Supplementary Material*.

The SUCRA scores – an approximation of the frequentist p-score, calculated using Bayesian statistics – show the network ranking of treatments in Figure 5. Olanzapine with SUCRA score 0.97 outranks all other treatments, with second best MA_H, 0.90, anamorelin 0.72, diet supplementation 0.56, cyproheptadine 0.48, mirtazapine 0.52, MA low dose, 0.58, other antidepressants 0.42, steroids 0.49, cannabinoids 0.18, treatment as usual 0.15, and placebo 0.02.

Meta-regression was performed by a series of artificial neural networks (ANN) using the multilayer perceptron. The last activation

function at the output layer was the hyperbolic tangent. The network was trained using cross-entropy (log class) due to the model's complexity, as it represented a non-linear variant of multinomial logistic regression. In Figure 6, we can see the layout of one of the neural nets. Neural net detailed calculations and outputs are included in the *Supplementary Material*. Drugs that resulted in satisfactory clinical effects were off-label treatments, licensed for other diseases. The weight increase in intervention groups was a result of ADR. Anamorelin, a ghrelin analogue, assumed to be orexigenic, performed relatively well, but olanzapine performed the best.

Discussion

Steiner *et al*., in a systematic review of hospitalized older adults, comparing the cannabinoid dronabilone, MA, and mirtazapine, reported that, based on reviewed studies, it is unclear if appetite stimulants have a significant effect as anorexia treatments.[16] A significant number of studies included mixed patient populations in terms of ages and diagnoses. Final sample sizes were small, there were large attrition rates, medication doses and duration of treatment were inconsistent, or not clearly discussed. Validating and reporting tools were not standardized; subjective measurements such as appetite improvement needed to be standardized to allow for result generalizability.

Mulchandani *et al.*, in a systematic review of older adults with anorexia and ARFID between 66-94 years old, reported that out of the 33 patients, 22 gained weight with pharmacotherapy, which included mirtazapine, bupropion, paroxetine, chlorpromazine and insulin, alprazolam, lorazepam, clorazepate, and venlafaxine.[41] Weight gain varied substantially between 1 and 10 kg.

McMaster *et al*., in a meta-analysis of dietary interventions with a total of 580 anorectic adult participants, reported that they did not reach any conclusions about treatment efficiency.[42]

Studies exploring the effect of olanzapine in older adults report appetite and weight increase, positive mood alterations in terms of depression and anxiety, and improved sleep.[43-46]

For older adults with or without dementia, nutritional supplementation was effective, but it was difficult to reach firm conclusions because of polypharmacy and insufficient information about medication doses, conditions, length of treatment, and nutritional plans.[47,48]

Our NMA subgroup analysis for older adults indicates that olanzapine first and cyproheptadine second may be beneficial at low

Table 1. Summary of studies, interventions, and patient characteristics included in the network. Intervention and control groups are shown per patient type.

Treatments summary	Patient group	Intervention group completers/total	Control group completers/total
Adults with chronic illness			
Megestrol acetate *vs.* placebo Cyproheptadine *vs.* placebo	Cystic fibrosis 3 studies – 3 RCTs 78 patients	85.7% 24/28	86.7% 26/30
Cyproheptadine *vs.* placebo Cannabinoids *vs.* placebo Megestrol acetate high dose *vs.* Megestrol acetate low dose Megestrol acetate *vs.* other steroids Olanzapine *vs.* other antipsychotics	HIV 10 studies – 9 RCTs, 1 retr cohort 926 patients	78.15% 354/453	73.74% 323/438
Anamorelin *vs.* placebo Cyproheptadine *vs.* placebo Cannabinoids *vs.* placebo Nabilone *vs.* dronabilone Mirtazapine *vs.* megestrol acetate Megestrol acetate high dose *vs.* megestrol acetate low dose Megestrol acetate *vs.* other steroids Megestrol acetate *vs.* placebo Nutritional support *vs.* megestrol acetate Olanzapine *vs.* placebo	Cancer – all cancers 31 studies 2 open-label trials 2 retr. cohorts 27 RCTs 5549 patients	77.5% 2253/2906	77.3% 1952/2524
Megestrol acetate *vs.* placebo	COPD 2 studies – 2 RCTs183 patients	89.01%81/91	84.8%78/92
Older adults with mixed chronic illness – cancer, chronic obstructive pulmonary disease, with/without dementia			
Anti-depressants *vs.* placebo Cyproheptadine *vs.* placebo Cannabinoids *vs.* placebo Nabilone *vs.* dronabilone Megestrol acetate *vs.* placebo Mirtazapine *vs.* antidepressants Nutritional supplementation *vs.* placebo Olanzapine *vs.* placebo Olanzapine *vs.* antidepressants	Older adults 30 studies – 20 RCTs 5 retr cohorts 2 case series 3 open-label trials 9674 patients	96.7% 4428/4577	86.1% 4390/5097

RCTs, randomized controlled trials; retr, retrospective.

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Table 2. Netranking of anorexia treatments in the network. Smaller p-scores indicate a more successful treatment.

Anorexia treatment ranking
tau² = 0.0389; tau = 0.1972; I² = 51.3% [35.0%; 63.4%]; p<0.0001
Power prior of 0.05 for the non-RCT component
Tests of heterogeneity (within designs) and inconsistency (between designs): Q, d.f., p-value
Total 129.25, 63, <0.0001
Within designs 105.94, 50, <0.0001
Between designs 23.31, 13, 0.0381

Treatment	p
Olanzapine	0.03
Megestrol acetate high doses	0.09
Anamorelin – ghrelin analogues	0.28
Megestrol acetate low doses	0.42
Diet supplementation	0.44
Mirtazapine	0.47
Steroids	0.51
Cyproheptadine	0.52
All other antidepressants (except mirtazapine)	0.58
Cannabinoids	0.82
Treatment as usual	0.85
Placebo	0.97

tau², tau-squared (τ^2) statistic; df, degrees of freedom; I², I-squared statistic; p, probability; Q, Cochran's Q statistic; RCT, randomized control trial.

doses; however, there were not enough published studies. Furthermore, lack of proper frailty and nutritional assessment tools, polypharmacy, mixed conditions, unclear or inadequate reporting in most published studies, increased inconsistency and uncertainty in the network, and as such, there can be no definitive conclusions.

McTavish *et al*., in a Cochrane meta-analysis for CF patients with anorexia comparing cyproheptadine hydrochloride and MA, concluded that both stimulants have similar weight increase results, but more research is needed, as the evidence of published studies is of low GRADE quality.[49]

We were unable to reach any statistically significant conclusions for adult patients with CF, due to a lack of published literature. Our findings show that both appetite stimulants used – cyproheptadine hydrochloride – and MA had similar moderate weight increase effects.[49-52] Studies with cannabinoids (dronabilone, nabilone) reported conflicting results: doses and treatments varied; therefore, reaching a valid conclusion was not possible.[12,53-56] Low ghrelin levels have been reported for patients with CF.[57] Based on treatment comparisons and results from this NMA, it is suggested that ghrelin agonists should be explored further as a possible treatment for such patients.

Bilbao *et al*.,[53] in a systematic review, reported that AIDS patients with anorexia treated with dronabilone had a 37.5% weight increase as opposed to 17.5% when treated with a placebo. However, medication doses were not standardized, and there were inconsistencies in methodologies and reporting outcomes. In addition, opportunistic samples, varying treatment durations, and other patient comorbidities resulted in difficulty reaching statistically significant conclusions.[57]

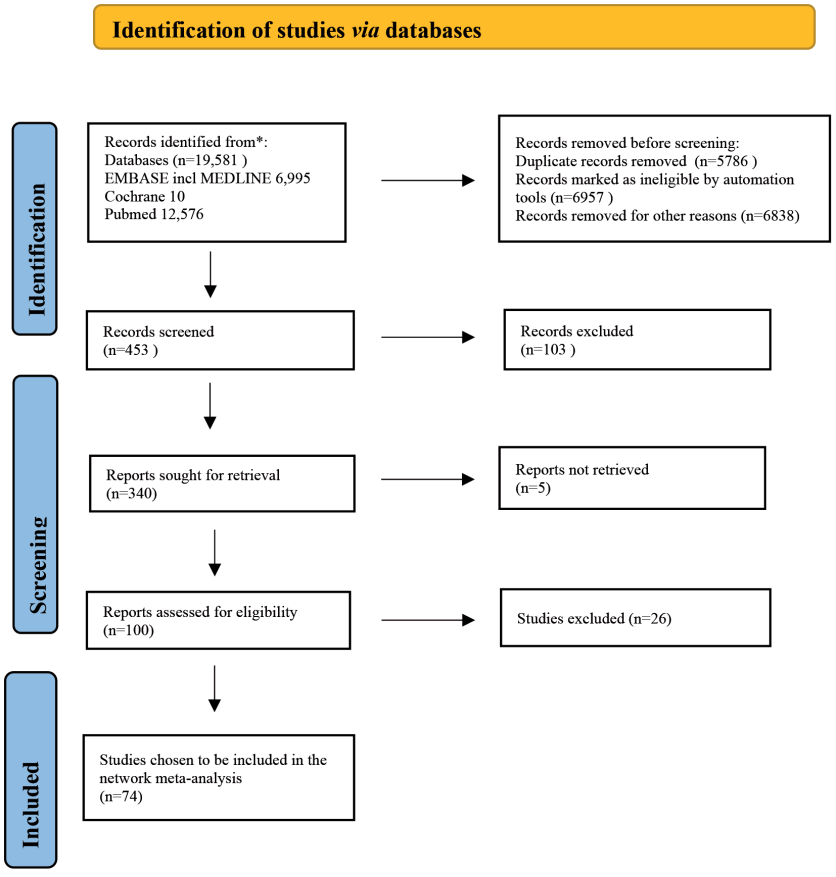


Figure 1. PRISMA-network meta-analysis flowchart.

Hammond *et al*. and Simon *et al*., in two meta-analyses about the orexigenic properties of cannabinoids [tetrahydrocannabinol (THC) and nabilone] in CA and HIV patients, reported that results were inconclusive about weight gain, but treatments improved appetite and immunomodulation.[12,54] Both reviews highlight low-quality evidence, inconsistencies in methodologies, reporting outcomes, opportunistic samples, different treatment doses and durations, and thus difficulty reaching conclusions.

Harrison *et al*.,[58] in a large systematic review with patient populations such as CA, HIV, irritable bowel syndrome, and post-gastric surgery treated with cyproheptadine, concluded that it is an effective appetite stimulant for but not effective in older populations (n=325), and not effective in HIV and CA patients.

Turcott *et al*. discussed anorexia and malnutrition in CA patients, which ranges from 25% to 70% as the disease progresses.[59] More than 65% of these patients experienced involuntary weight loss because of anorexia. Their systematic review considered patients treated with mirtazapine, cannabinoids (dronabilone, THC, nabilone), ghrelin agonists, olanzapine, and N3 fatty acid supplementation. Outcomes discussed were appetite, energy intake, weight or body composition changes, and taste alterations in patients with CA. Some patients treated with THC 2.5 mg daily had a 10% weight increase, followed by patients treated with mirtazapine, who had an average 1.2 kg weight increase in the first 4 weeks of treatment. Patients treated with olanzapine had a mean pooled BMI increase of 2%, those with ghrelin agonists of 1.8%, while the BMI increase for patients treated with N3 fatty acid supplementation was inconclusive. In addition, patients treated with dronabilone had a mean pooled BMI increase of 2.4%.

Lim *et al*.,[11] in a large meta-analysis with CA patients treated with MA, concluded that MA is effective in anorectic CA patients but has side effects such as thromboembolism, constipation, edema, and somnolism. Studies were divided into two categories: patients treated with MA doses greater than 320 mg/day and patients treated with doses lower than or equal to 320 mg/day. The mean pooled weight change for all studies was 0.75 kg. Higher MA dose resulted in weight loss, and patients with advanced CA did not benefit from MA treatment.

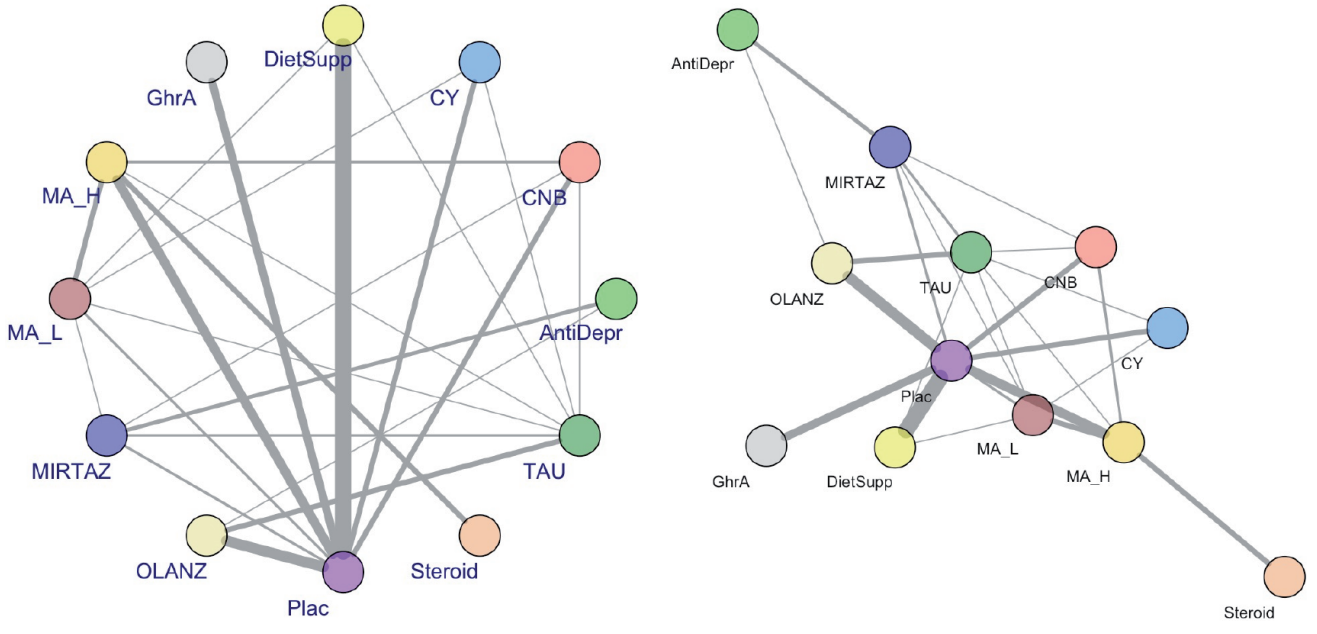
Sae-Teaw *et al.*[60] in a large NMA compared the effectiveness of MA *vs.* anamorelin, a ghrelin agonist, MA, and medroxyprogesterone in CA, HIV, and mixed population patients of 10,579 patients. The conclusion was that high-dose MA as well as short-term treatment with corticosteroids increase weight in such patients. In addition, anamorelin has good results in cachexia treatment, contributing *via* appetite stimulation to weight gain. Anamorelin has been approved in Japan since 2020 as an anorexia treatment for certain types of CA patients.

Ruiz-Garcia *et al*.,[13] in a Cochrane meta-analysis on treatment efficacy of MA in CA patients (n=3,963) and controls (n=3180), reported that MA was effective in weight increase but could not conclude on optimal therapeutic treatment doses.

The ROMANA trials studied the effectiveness of anamorelin as an appetite stimulant for CA patients.[61] There were two trials that tested this part, and a third trial that tested safety.[62] Although there were some interesting outcomes in terms of weight increase due to lean body mass and appetite improvement, it did not improve strength or function.

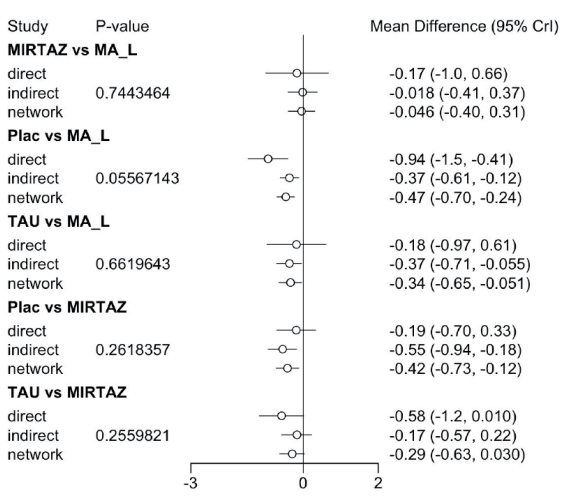
Anamorelin in low doses has been used in older adults with a good tolerability profile, but there are no reported outcomes in terms of appetite/weight improvement.[63,64]

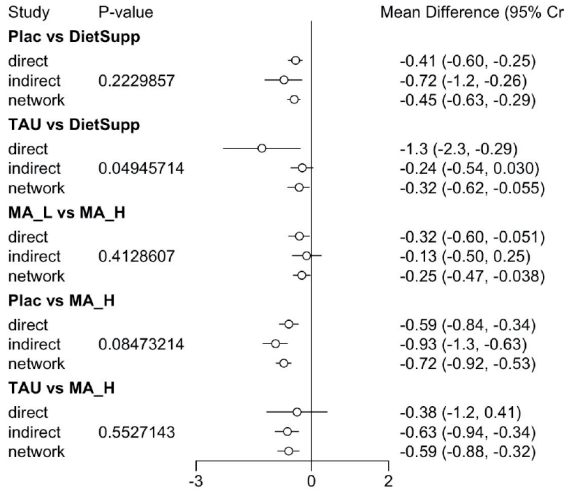
Olanzapine has been extensively studied as a treatment for anorectic patients over the last 30 years.[65] It has been recently approved in Norway for CA-related anorexia/cachexia, and it is in the latest American Society of Clinical Oncology guidelines as a recommended treatment.[66]

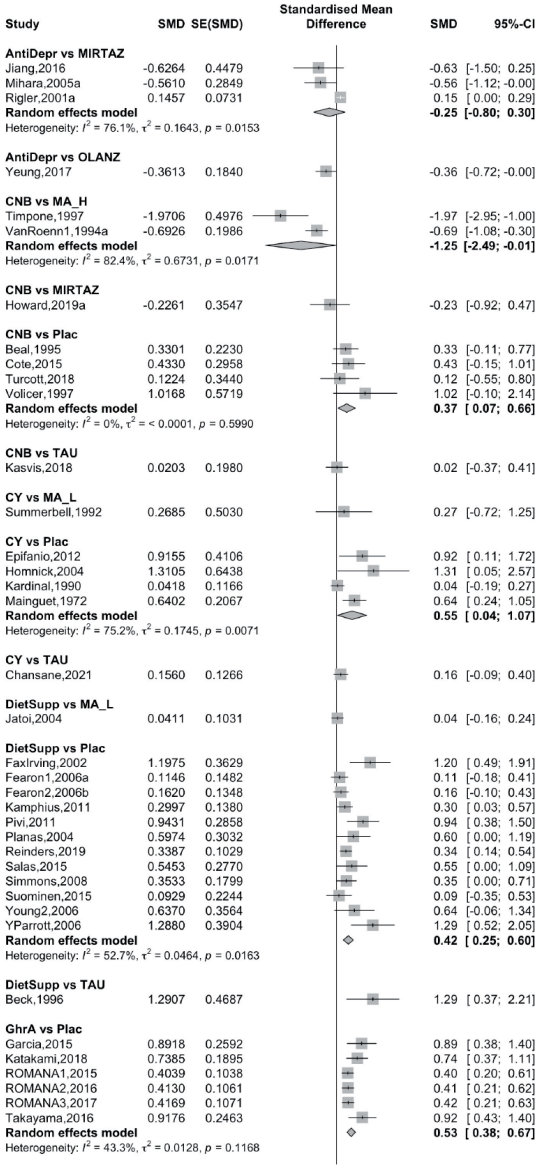


A. **B.**

Figure 2. Anorexia treatments network meta-analysis geometry. A) Entire network layout; B) layout as per Fruchterman-Reingold algorithm. AntiDepr, antidepressants – all classes except mirtazapine; CNB, cannabinoids (dronabilone and nabilone); CY, cyproheptadine; DietSupp, diet supplementation; GhrA, ghrelin analogues (anamorelin); MA_H, megestrol acetate high dose; MA_L, megestrol acetate low dose; MIRTAZ, mirtazapine; OLANZ, olanzapine; Plac, placebo; TAU, treatment as usual; Steroid, corticosteroids.







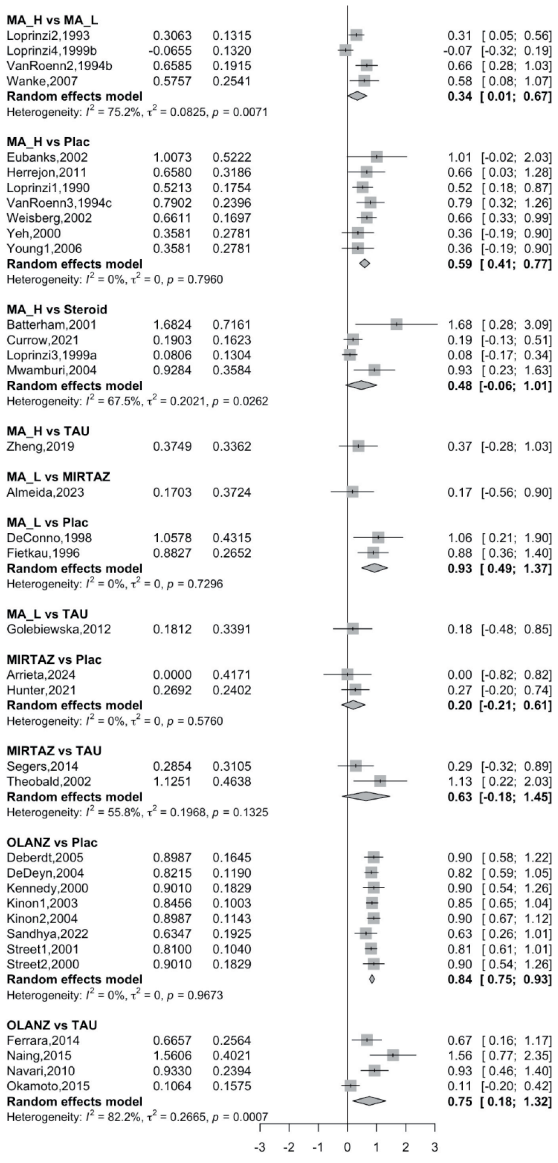


Figure 3. Individual Studies grouped per intervention type, with p-scores as calculated by the frequentist analysis. AntiDepr, antidepressants – all classes except mirtazapine; CNB, cannabinoids (dronabilone and nabilone); CY, cyproheptadine; DietSupp, diet supplementation; GhrA, ghrelin analogues (anamorelin); MA_H, megestrol acetate high dose; MA_L, megestrol acetate low dose; MIRTAZ, mirtazapine; OLANZ, olanzapine; Plac, placebo; TAU, treatment as usual; Steroid, corticosteroids.

Okamoto *et al*. reported that a low dose of olanzapine up to 2.5 mg daily increased appetite by 149% in 80 CA patients,[67] while Singuluri *et al.* reported a greater than 5% weight increase in 60% of treated patients.[68]

Most studies highlight the low quality and non-standardization of reporting evidence, inconsistencies in measurements, doses, illness and treatment durations, interpretations, and outcomes, as well as the need for alternative approaches to anorexia treatments.

For CA patients, there were similar challenges in terms of medication treatments, doses, and reporting outcomes; however, collected data were enough to conclude that olanzapine low dose, MA high dose, and anamorelin 100 mg improve appetite and weight in these patients.[2,5,10-12,54-56,58,59,62,65-75] Olanzapine specifically had the least side effects, at the smallest doses (doses ranging from 2.5-5 mg per day). MA (doses from 800-850mg per day) resulted in weight gain, but unfortunately, numerous side effects such as thrombosis, pulmonary embolism, fractures, skin thinning, mood changes, and deaths.[51,70-72] Anamorelin resulted in weight gain, with significantly fewer side effects (dizziness, malaise, nausea, hyperglycaemia).[2,62]

Studies comparing the effects of anorexia on patients of organic and non-organic origin suggest that both groups are affected in similar major domains: body weight, body composition (muscle, bone, adipose tissue), metabolism, neurotransmitter function, inflammation, and mortality. Patients with anorexia may develop cachexia or sarcopenia, and without treatment, are at high risk of death. Pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-1β have been identified across all anorexia types and are considered potential biomarkers.[15,76] Recently, there has been a growing interest in the role of gut microbiota in the pathogenesis of anorexia nervosa,[18,77] though caution is needed in this area due to the abnormal eating habits of these patients, which may lead to altered gastrointestinal metabolism.

Drug-induced weight gain is a well-documented ADR.[78-80] Nearly all pharmacotherapies currently used to treat anorexia – including anorexia nervosa, regardless of subtype – rely on ADRs, with the notable exception of ghrelin agonists.

Numerous studies have confirmed that pharmacogenomics play a significant role in weight gain associated with specific drugs, including corticosteroids, synthetic hormones, cannabinoids, antipsychotics, antidepressants, antiepileptics, β-blockers, and antidiabetic medications.[78]

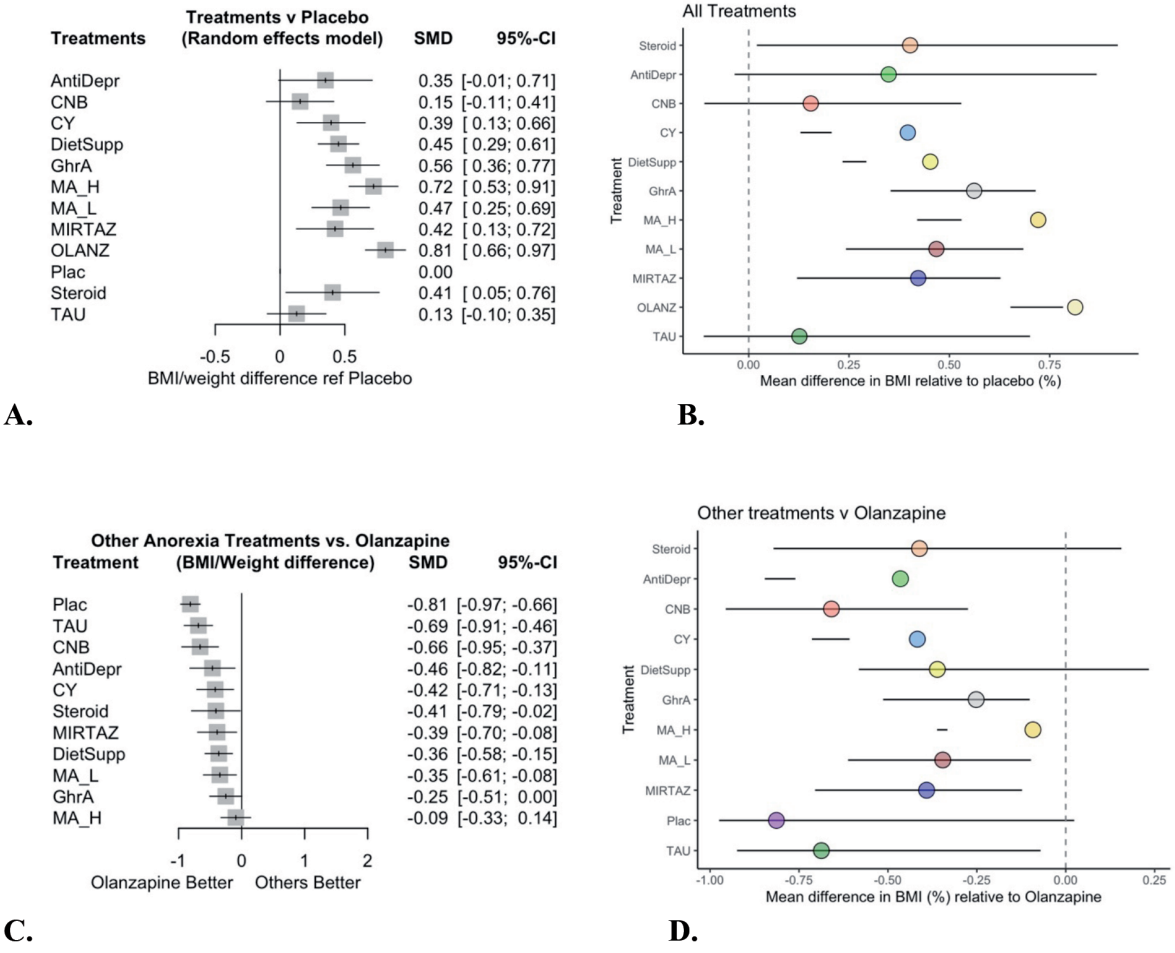


Figure 4. Anorexia treatments –analysis for all patients relative to placebo. A) Relative to placebo, frequentist analysis; B) relative to placebo, Bayesian analysis; C) olanzapine treatment for anorexia subgroup analysis for cancer patients compared to all other treatments, frequentist analysis; (D) Bayesian analysis. Both analyses highlighted olanzapine as the most effective treatment with regard to BMI/Weight changes. There were non-significant differences in p-scores between the two statistical analyses. AntiDepr, antidepressants – all classes except mirtazapine; CNB, cannabinoids (dronabilone and nabilone); CY, cyproheptadine; DietSupp, diet supplementation; GhrA, ghrelin analogues (anamorelin); MA_H, megestrol acetate high dose; MA_L, megestrol acetate low dose; MIRTAZ, mirtazapine; OLANZ, olanzapine; Plac, placebo; Steroid, corticosteroids.

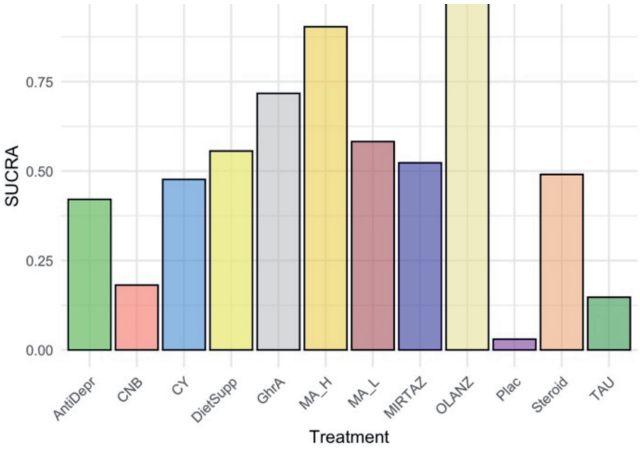


Figure 5. Anorexia treatments: surface under the cumulative ranking (SUCRA) scores, Bayesian analysis, treatment ranking. Olanzapine is the most efficacious treatment with regard to body mass index/weight changes. AntiDepr, antidepressants – all classes except mirtazapine; CNB, cannabinoids (dronabilone and nabilone); CY, cyproheptadine; DietSupp, diet supplementation; GhrA, ghrelin analogues (anamorelin); MA_H, megestrol acetate high dose; MA_L, megestrol acetate low dose; MIRTAZ, mirtazapine; OLANZ, olanzapine; Plac, placebo; TAU, treatment as usual; Steroid, corticosteroids.

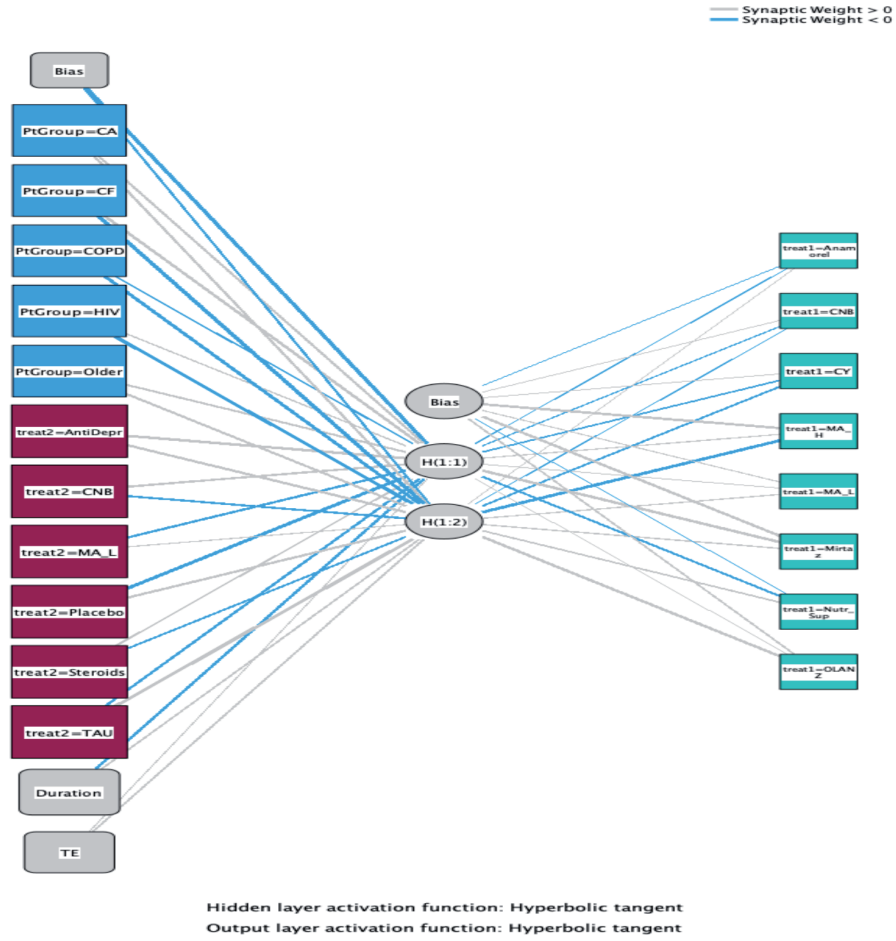


Figure 6. Neural net, based on the multilayer perceptron. Inputs are the entire network meta-analysis dataset. Covariates are TE (Hedge's g of each study) and duration of treatment. Factors are patient group [cancer (CA), HIV, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), older adults] and comparison treatment (treat2), output is intervention type (treat1 - olanzapine, mitrazapine, megestrol acetate high, and low doses, anamorelin, nutritional support, cannabinoids, antidepressants (other than mirtazapine). The rescaling method of covariates was adjusted-normalised. The hidden and output layer activation function was the hyperbolic tangent. The thickness of interconnecting lines represents the significance of synaptic weights; the colour blue is for synaptic weights <0, whilst the colour grey is for synaptic weights > 0. Synaptic weights govern transformation and information propagation through the artificial neural net (ANN), by adjusting the weights, so the ANN learns patterns and performs various tasks (regression, classification, prediction). Duration = treatment duration in weeks. The network classified treatment success based on treat1 with 100% precision. The mode of action was adverse drug reaction. DIET, dietetic interventions; GhrA, ghrelin analogue – anamorelin; AntiDepr, antidepressants – all classes except mirtazapine; CNB, cannabinoids (dronabilone and nabilone); CY, cyproheptadine; Nutr_Supp, diet supplementation; GhrA, ghrelin analogues (anamorelin); MA_H, megestrol acetate high dose; MA_L, megestrol acetate low dose; MIRTAZ, mirtazapine; OLANZ, olanzapine; Plac, placebo; TAU, treatment as usual; Steroid, corticosteroids.

Genomic loci linked to antipsychotic-induced weight gain include the genotypic and allelic frequencies of *CNR1* (rs1049353) and *INSIG2* (rs7566605, rs78310016), as well as the genetic-epigenetic modulation of the *CRTC1* gene.[80,81] Other relevant loci include the Met/Met genotype of BDNF Val66Met, the Val/Val genotype, and the Val66Met-rs1519480 G/A haplotype and Val66Met-rs11030101.[82] Patients carrying these genetic variations tend to experience significant weight gain when treated with specific antipsychotics. In the case of olanzapine, polymorphisms in *CYP2C9* phenotype, *SLC22A1*, and *APOC3* polymorphism were related to variability in its pharmacokinetics.[83]

The gut-brain axis is a communication network that connects the gastrointestinal system and the central nervous system. As a result, the gut and the brain affect each other through complex neuroendriconological and metabolic mechanisms. This bilateral network is important in neuroinflammation as well as the orexigenic axis and has been linked to anorexia nervosa,[84,85] mood disorders, neurodevelopmental and neurodegenerative disorders, as well as irritable bowel syndrome.[14,15,86]

Microbiota alterations have been associated with metabolic dysfunctions and specifically in weight gain, as well as triglycerides, glycemic levels, and proinflammatory cytokine expression.[87]

The antipsychotic olanzapine, specifically, can alter gut microbiota homeostasis, which can lead to a decrease in the short-chain fatty acids.[88,89] As a result, the secretion of serotonin in the gut is decreased and which stimulates the orexigenic axis, and the ratio of neuropeptide Y/agouti-related peptide, which contributes to lipid deposition. This means that olanzapine, like most antipsychotic drugs, increases lipid biosynthesis through alterations in gene expression.[90]

Recent studies report that olanzapine, which is used as an antiemetic for chemotherapy-induced nausea and vomiting,[65] reduces CA cell survivin expression in glioblastoma,[91] lung,[92] and pancreatic CA, as well as some types of ovarian in breast CA.[93] In addition, it has been shown to sensitize CA stem cells to chemotherapeutic agents and to inhibit tumorigenesis and chemoresistance. In CA patients, specifically, it has also been found to reverse agitation, anxiety, depression, and to promote better sleep.[94]

Conclusions

The mechanisms underlying anorexia are highly complex, and the precise neurochemical pathways involved remain to be fully understood. While pharmacogenetics has proven valuable in identifying factors that contribute to successful treatments, additional research is needed to pinpoint specific genetic variations that could guide the development of new, more effective therapies. The gut-brain axis and its significance in personalized medicine treatments should be researched further. Drug repositioning of olanzapine and anamorelin should be explored further in CA-related anorexia. Could ghrelin agonists be used to improve appetite in CF, HIV/AIDS, or the elderly? Low-dose anamorelin in elderly patients was well tolerated in studies.[2,39]

ANNs can capture non-linear relationships in treatment outcomes and can be useful in outlining key factors influencing treatment success or failure. These networks can provide invaluable insights by identifying which variables most strongly affect treatment outcomes, thereby informing clinical practice and improving the personalization of treatment strategies.

Limitations

Every effort was made to ensure the accuracy of the data used in this analysis. Many studies were excluded due to the absence of control groups, poorly defined outcomes, or potential publication bias. Studies with mixed-age patient populations were also excluded. It is acknowledged that the generated results and conclusions would have been more robust if a larger number of studies had been included.

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Online supplementary material:

Supplementary Material. Reviewed studies, sensitivity analysis, additional network results, CINeMA estimations, and neural net meta-regressions.