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Review
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Network Meta-Analysis of Anorexia Nervosa Treatments: Toward Precision Medicine with Pharmacogenomics and Neural Nets

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ABSTRACT

Objective: Anorexia nervosa (AN) affects millions of people worldwide and treatments vary widely with no set treatment guidelines. A network meta-analysis compared and contrasted treatments for adults with AN that reported body mass index (BMI) or weight changes.

Methods: Embase, Medline, CINAHL, PubMed, PsycINFO, Cochrane, and clinicaltrials.gov were searched, from January 1974 to March 2024, for articles reporting weight or BMI results pre/posttreatment for anorexia treatments. Outcomes, using pooled-weighted-standard mean effect sizes and subgroup analyses per-intervention-type, were analyzed using a random effects model with bayesian and frequentist statistics. Artificial neural nets were used to predict response to future treatments. About 63 studies were included out of the 650 reviewed articles.

Results: The random effects model calculated a pooled-weighted-effect size for 4366 patients of 1.43 (1.00-1.86) 95%CI for surgically invasive neuromodulation (deep brain stimulation (DBS) and Capsulotomy Surgery), 0.65, 95%CI (0.45-0.86) for pharmacological interventions, 0.10 (0.23-0.42) for non-invasive neuromodulation (repetitive transcranial magnetic stimulation, transcranial direct current stimulation, electroshock treatment), −0.02 (−0.32-0.29) for psychotherapeutic interventions, and −0.09 (−0.47-0.29) for compulsory diets. Between-study heterogeneity was $tau^2 = 0.08$.

Conclusion: Subgroup analysis suggests that capsulotomy, DBS, olanzapine, and cyproheptadine may result in higher BMI/weight differences and longer posttreatment weight maintenance. Meta-regression with neural nets indicates that the mode of action of interventions, resulting in adverse drug reactions for some patients with specific pharmacogenetic profiles, has a higher chance of affecting treatment outcomes. These findings suggest that pharmacogenomic testing and precision medicine need to be explored further for AN patients.

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Keywords: Anorexia nervosa, pharmacogenomics, network meta-analysis, neural nets, gut microbiota, Olanzapine

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INTRODUCTION

Eating disorders include anorexia nervosa (AN), bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, rumination-regurgitation disorder, and other specified feeding or eating disorders, according to the International Diagnostic Disease Manual (ICD) 11th edition. Two AN subtypes of note are restrictive type (AN-R) and binging-purging type (AN-BP). Anorexia nervosa restrictive type is characterized by low-weight, food restriction, weight-loss inducing behaviors, with or without increasing energy expenditure, but without binging or purging behaviors. Similarly, AN-BP fulfils all the above criteria with the addition of bingeing and purging cycles, as well as restrictive tendencies. Severe and enduring anorexia nervosa (SE-AN) is another classification with the above subtypes.[1]

Anorexia nervosa prevalence in females is estimated to be up to 3%. New data indicates that lifetime AN prevalence in females can be up to 6% and up to 4% in males. According to world statistics, more than 3.3 million healthy life years are lost worldwide because of eating disorders.[2]

About 5% of AN patients die within 4 years of the diagnosis. Anorexia nervosa has one of the highest mortality rates amongst eating disorders with a standardized mortality ratio (SMR) of 5.9 (95% CI 4.2-8.3) for all sexes combined.[3]

Although there is no set treatment guidelines for AN in most countries, many studies report that the majority of patients are treated pharmacologically. Drugs used range from antipsychotics to antidepressants, mood stabilisers, antihistamines, corticosteroids, synthetic progestins, cannabinoids, psychedelics, and anti-diabetic agents. Such treatments are not licensed for anorexia and rely solely on the mode of action of drugs (MOA) and adverse drug reactions (ADRs).[4]

Gut microbiota are believed to be 1 potential therapeutic target, but data are lacking in humans. However, there are increasingly more studies reporting altered gut microbiota in AN, linked to genetic loci.[5]

Nutritional support whilst necessary has limited efficiency and results are not lasting.[6] Anorexia nervosa patients are usually treated with psychotherapies, with or without pharmacotherapies, compulsory feeding, and nasogastric tube (NG) feeding.[7] However, these treatments are addressing symptoms and not actual disease causes.

A significant proportion of AN patients have other psychiatric comorbidities such as depression, obsessive compulsive disorder, trauma, or anxiety. Psychotherapeutic support can be helpful but has no lasting effects.[8] Many studies have identified biochemical imbalances, brain changes, genetic polymorphism, genomic factors, and altered neuroendocrinology in these patients.[9]

The lack of specific clinical guidelines allows for a variety of off-label treatments that are shown to be effective short-term. Neuromodulation therapies such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and neurosurgical approaches, such as capsulotomy and deep brain stimulation (DBS), are sometimes used for AN patients, even if they are highly experimental.[10]

This study compares and contrasts selected AN interventions who reported body mass index (BMI)/weight outcomes. There is emerging, statistically significant evidence, highlighting their critical role and impact on morbidity and mortality outcomes.[11] Treatments with higher probability of affecting outcomes are presented, and recommendations about future directions are discussed.

METHODS

Search Strategy and Study Selection

Systematic review and a network meta-analysis (NMA) of selected AN treatments were conducted as per the PRISMA-NMA guidelines.[12] Changes in weight and/or BMI were identified as primary outcomes for inclusion. Secondary outcomes were noted, but due to multiple reporting instruments, they could not be analyzed. The random effects model used the weight-corrected standardized mean difference, since selected studies assessed the same outcome but used different measurement criteria.

Databases searched were EMBASE, MEDLINE, CINAHL, PsycINFO, Cochrane, PubMed, and clinicaltrials.gov. Search criteria were AN interventions in the last 50 years (first search January 15, 2023, last search March 14, 2024). The decision to include this wide time-range in this NMA was in order to increase statistical power, produce more generalizable results, observe historic trends in treatments, and thus enhance understanding of the topic. Excluding older studies can lead to time-lag bias which may affect result validity.[13] To account for inconsistencies introduced by changes in measurements, diagnostic criteria, possible lower quality of data in older studies, and study heterogeneity, extensive statistical analysis was carried out.

There were no ethnic, language, or geographical restrictions in the search strategy. The same query terms and inclusion criteria were used across all searched databases. References were exported and combined in a single Endnote Library, where duplicates were removed.

Study designs for review were RCTs, systematic reviews, meta-analyses, network meta-analyses, and real-world data such as cohort studies, open-label trials, case reports and case series, published in evidence-based medicine peer-reviewed journals. Incomplete and unpublished studies were excluded. Studies included in the final NMA were RCTs and real-world evidence.

Identified studies were loaded onto Covidence, a web-based tool for collaborative reviews, where they underwent a second screening process. Studies were equally divided amongst all authors for an initial independent review, using the voting function in Covidence. Random control trials were selected if the revised Cochrane tool of bias was part of the design or were assessed as low bias. Systematic reviews and meta-analyses were assessed with AMSTAR-2. Non-RCTs were assessed with ROBINS-I V2.[14]

Differences of opinions were jointly discussed, and studies were advanced to the extraction stage by majority consensus. Risk-of-bias assessments can be seen in the supplement, in the reviewed studies section, under the column "Risk of Bias."

The Confidence in Network Meta-Analysis (CINeMA)[15] framework (based on GRADE-2) as per Cochrane guidelines[16] was used to assess the quality of evidence for within-study bias, reporting

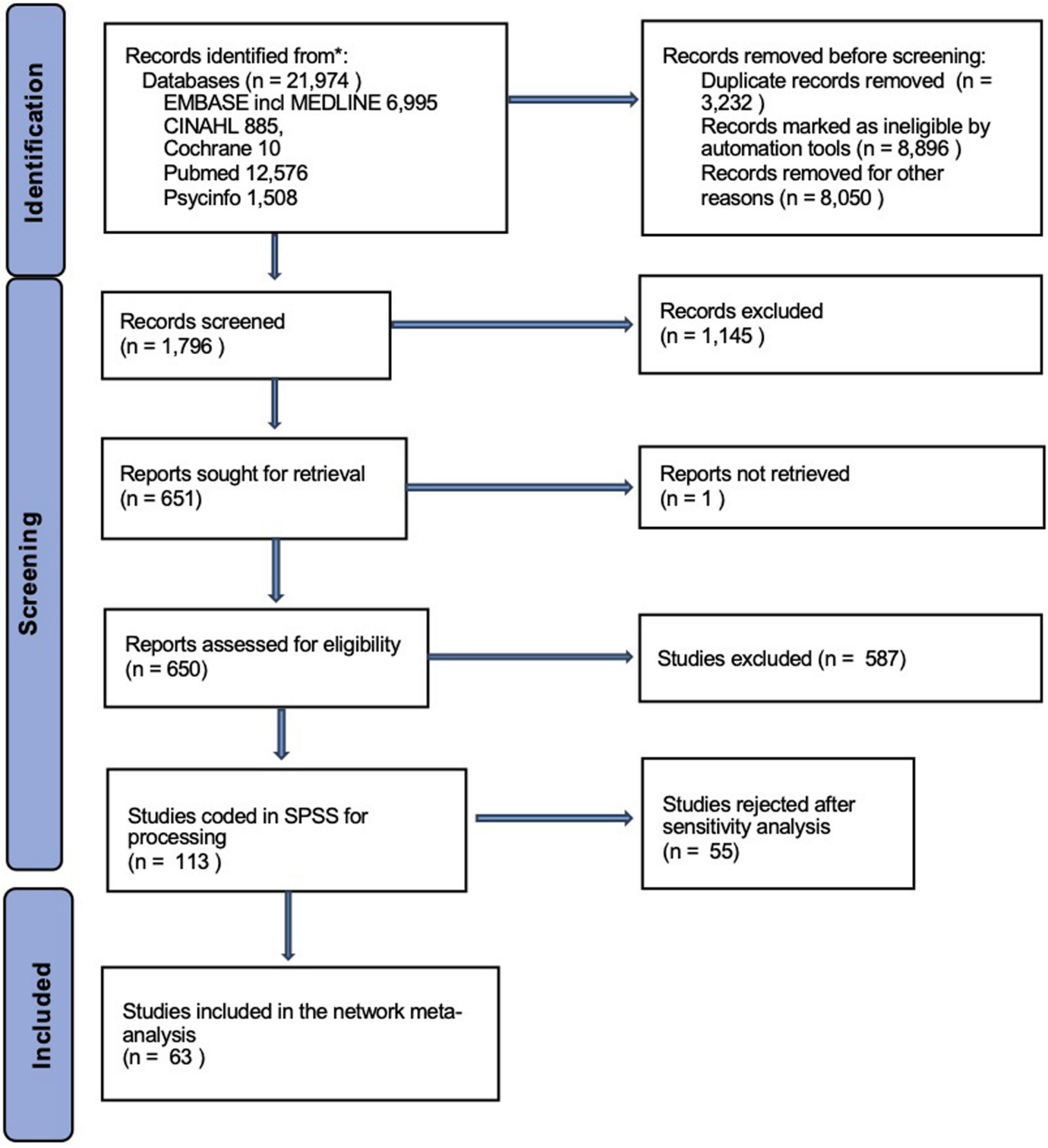
bias, direct/indirect comparisons of included studies in the network, indirectness, imprecision, heterogeneity, and incoherence. The GRADE-2 CINeMA classifications are included in the supplement section.

Full list of search arguments, criteria, study characteristics, designs, results, and additional CINeMA estimates can be seen in the supplement section.

The Prisma-NMA Flowchart showing study selection can be seen in Flowchart 1.

Eligibility Criteria

Patient population was adults older than 18 years with either International Diagnostic Disease Manual (ICD)-10/11, DSM IV/V, or clinical diagnosis of AN. About 94% of studies included a mix of AN-R, AN-BP, and SE-AN, and AN where the type was not specified (coded



Flowchart 1. PRISMA-Network Meta-analysis Flowchart of Included Studies for Anorexia Nervosa Network Meta-Analysis.

in SPSS/R as AN-unspecified). Few studies had strict inclusion criteria for the AN-R subtype (see Table 1). All patient data were anonymous, openly available online, and had been previously published in peer-reviewed manuscripts. No new patient data were used.

Data Extraction and Synthesis

It was unanimously agreed to incorporate real-world data such as cohort studies, case series, retrospective studies, and register studies that are traditionally ignored in older types of NMAs. The incorporation of such data is a new method for NMAs, particularly useful where quality RCTs are lacking.[17] To penalize and control the contribution of these data, account for the bias due to mixed AN severity and subtypes, treatment groupings, as well as reduce type I and II errors, elastic meta-analytic predictive priors were used for the bayesian models and lasso l1 for the frequentist.[18]

Individual participant data (IPD) were requested from study authors, when not already published as datasets. Individual participant data analysis allows for investigating how treatments vary over longer periods of times. It facilitates direct examination of patient characteristics, improves consistency across treatment outcomes, and enhances statistical power and precision. In addition, variables and analyses can be standardized, more complex relationships can be investigated, and results are deemed more generalizable.[19]

Statistical Coding and Analysis

Treatments analyzed were grouped into 4 main categories:

1. Pharmacotherapies with antidepressants, antipsychotics, cannabinoids, antihistamines, hallucinogenics, and ghrelin agonists. Only antidepressants, antipsychotics and antihistamines, however, were included in the NMA, as other drug types like relamorelin (ghrelin agonist), dronabilon (cannabinoid), and psylocibin (hallucinogenic) were excluded due to insufficient studies.
2. Psychotherapies—Cognitive behavioral therapy enhanced for AN (CBT-E), cognitive remediation therapy (CRT), family behavioral therapy (FT), and Maudsley model of AN treatment for adults (MANTRA). Internet-delivered psychotherapies were reviewed but not included due to insufficient studies.
3. Neuromodulation—Capsulotomy surgery, DBS, rTMS, tDCS, and electroconvulsive therapy (ECT). Subdivided into surgically invasive (capsulotomy and DBS) and non-invasive (rTMS, tDCS, ECT).
4. Feeding/dietetic interventions, voluntary, compulsory, with or without NG tube and diet supplementation.

Studies were coded per type (random control trials (RCTs) or real-world evidence), duration, mode of action, researcher, year, patient group, patient age, number of patients at the start and end for both intervention and control groups and weight/BMI before and after treatment, for all groups. The risk of bias classification was added, as well as follow-up duration in weeks and country of origin.

Data were loaded onto IBM SPSS v30 for further processing. Hedge's g effect sizes based on BMI or weight variations pre/posttreatment were calculated by SPSS, for each study, and per treatment type, using IPD.

The resulting SPSS dataset was used as input to R (v.4.3.3), artificial neural nets (ANNs), and CINeMA in order to conduct sensitivity analysis, treatment effect comparison, and meta-regression.

Network meta-analysis outputs were verified with Python version 3.12, SPSS version 30.0 (IBM SPSS Corp.; Armonk, NY, USA), and CINeMA to ensure accuracy, since custom R code was developed for this NMA. Final best-fitted model selection and testing was automated in R, based on evidence-based statistical criteria for NMAs.

Sensitivity Analysis

A statistical research strategy based on methodological triangulation and meta-regression was used to cross-verify NMA results. Models (a) and (b) were run in R. Extensive sensitivity analyses were performed

Table 1. Treatments, Study Types and Characteristics

Treatment	Study Types	AN Characteristics	Intervention Group	Control Group
Psychotherapies	12 RCTs, 3 Cohort Studies (CBT-E, CRT, FT, MANTRA) CBT-E—8 RCTs, 1 Cohort CRT—3 RCTs MANTRA—in 3 RCTs FT—in 2 RCTs	8 RCTs, AN-R and AN-BP 1 RCT-AN-R 2 RCTs, SE-AN 1 RCT and 1 Cohort Studies—AN-unspecified	82.1% (551/671)	78.8% (465/590)
Pharmacotherapies	Cyproheptadine—6 RCTs, Olanzapine—5 RCTs, 1 Open Label Antidepressants—3 RCTs	1 RCT—AN-R All others—AN-R and AN-BP	91.6% (533/582)	75.61% 403/533
Surgical treatments (DBS and capsulotomy)	DBS—1 Retrospective Cohort, 1 Longitudinal Study, 7 Case series Capsulotomy—3 Open label trials	4 studies—AN-R All other studies AN-R and AN-BP	95.3% (185/194)	–
Non-invasive neuromodulation (rTMS, tDCS, ECT)	rTMS—3 RCTs, 4 Open Label trials ECT—1 RCT, 1 Case series tDCS—3 RCTs	1 RCT—AN-R 1 RCT—AN unspecified All other studies AN-R and AN-BP	91.1% (154/169)	87.2% (89/102)
Feeding treatments (compulsory, voluntary)	3 RCTs, 3 Retrospective Cohorts, 2 Register studies	1 study—AN unspecified All other studies AN-R and AN-BP	98.7% (908/920)	98.6% (507/514)

Treatments, types of studies per category, anorexia nervosa characteristics and treatment completion rates per treatment type (completers/initial group size), for intervention and control groups. AN, anorexia nervosa; AN-unspecified, researchers did not describe the anorexia subtype; AN-BP, anorexia nervosa binging-purging type; AN-R, anorexia nervosa restrictive type; CBTE, cognitive behavioural therapy enhanced; CRT, cognitive remediation therapy; DBS, deep brain stimulation; ECT, electroshock treatment; FT, family therapy; MANTRA, the Maudsley model of anorexia nervosa treatment for adults; RCT, random control trial, antidepressants (fluoxetine); rTMS, repetitive transcranial magnetic stimulation; SE-AN, severe and enduring anorexia nervosa; tDCS, transcranial direct current stimulation

to determine, amongst other things, if the mixed disease AN severity, the non-RCT component in the network and the inclusion of a wide time-range of studies introduced heterogeneity, uncertainty and incoherence (55 studies were rejected from inclusion at that stage, by the models):

a. Bayesian hierarchical models with Monte-Carlo simulations with the Gibbs sampler and elastic priors to penalize contribution of historic data and non-RCTs.
b. Frequentist methods: To minimize bias, models were penalized for between study variance with the least-squares approximation (Lasso ℓ1-norm regularization).

Network meta-analysis outputs were verified by

• traditional cumulative meta-analysis with naïve effect pooling, using random-effects model, run on SPSS.

• CINeMA (NMA framework using frequentist methods).

Between-study heterogeneity was assessed with tau^2 and I^2. See supplement for more details.

Meta-Regression

Network meta-regression with ANNs was conducted to test if there were factors (covariates) that affected treatment efficiency, and if response to treatments could be predicted. Artificial neural nets can capture non-linear regression models that other types of frameworks do not. The null hypothesis was that patient response to treatment is not because of the intervention MOA resulting in ADRs (weight-gain), subject to individual genetic code variations.

A series of ANNs using backpropagation algorithms, modeled after the multilayer perceptron, were used to test which factors were statistically significant for treatment outcomes, as well as predict future treatment responses.

Detailed descriptions of the statistical methodologies used, ANN configurations, and results are included in the supplement section.

In Diagram 1 below, a method flow schematic outlines the authors' analytical approach. Note the use of different statistical methodologies (triangulation) to ensure result accuracy.

Effect Size Calculation

Treatment success was defined as per Cohen and Hedges,[20] with bias-corrected standard mean differences (SMD):

0.20 small effect

0.50 moderate effect

0.80 large effect

RESULTS

The total number of patients analyzed was 4366. There were 2579 patients in all intervention groups. Of those, 2306 patients completed treatments. There were 1655 patients in all control groups and 1401 completers. Types of studies, treatments, and treatment compliance per intervention type are summarized in Table 1.

In Table 2, frequentist NMA *P*-scores for each treatment category and subgroup analysis are presented.

Weighted pooled-effect sizes per treatment category can be seen in Figure 1A, as well as the NMA geometry in 2 configurations in Figure 1B. Surgically invasive neuromodulations (capsulotomy and DBS) appear to rank higher than the rest of AN treatments, followed by pharmacological treatments. Non-invasive neuromodulations (rTMS, tDCS, ECT) rank third, with psychotherapies, compulsory feeding, and specialist treatment as usual (specialist supportive clinical management (SSCM)) ranking in the bottom 3. Additional forest plots can be seen in the supplement section. The non-RCT network was penalized with elastic prior $P = .5$.

In Figure 2, individual studies are grouped by intervention type, as categorized by the NMA.

In Figure 3A, AN treatments are shown in terms of BMI/weight changes, with reference to placebo, by the frequentist subgroup analysis. In Figure 3B bayesian SUCRA scores, similarly, summarize treatment rankings. Both analyses estimate capsulotomy, DBS, and olanzapine amongst the 3 highest performing treatments.

Detailed treatment characteristics, additional results, and network estimates can be seen in the supplement section. All statistical analyses reached similar conclusions.

Meta-Regression

A series of feedforward neural nets were designed to run meta-regressions for the NMA. All coded study variables were initially tested together, as well as, in a stepwise approach as ANN inputs. Body mass index/weight fluctuations were defined as the ADR effect, since all treatments were off-label. The most statistically significant results are presented. In Figure 4A, the ANN classification of study characteristics affecting treatment outcomes is shown. The ANN estimated treatment duration, patient starting and ending BMI as characteristics that have a higher chance of affecting outcomes. Outputs were treatment effect (TE) and standard error of the effect size (seTE).

In Figure 4B, the second ANN used the covariates identified as more significant by the first ANN in Figure 4A to classify and predict which treatment MOA resulting in an ADR (or not) performed better or worse.

Figure 5A and B outline how the model predicted treatment performance, based on TE and seTE, per treatment type in Figure 5A and for all treatments together in Figure 5B.

Artificial neural nets identified the treatment MOA as the factor with the higher chance of affecting treatment outcomes with regards to BMI/weight changes, followed by treatment duration. This is shown in Figure 6A. The treatment with a higher probability of affecting treatment outcomes was Olanzapine. Artificial neural nets correctly penalized neurosurgical interventions that other analyses ranked amongst the highest, due to their wide confidence intervals and high standard error of effect-size values. Sensitivity and specificity for those results are shown in Figure 6B.

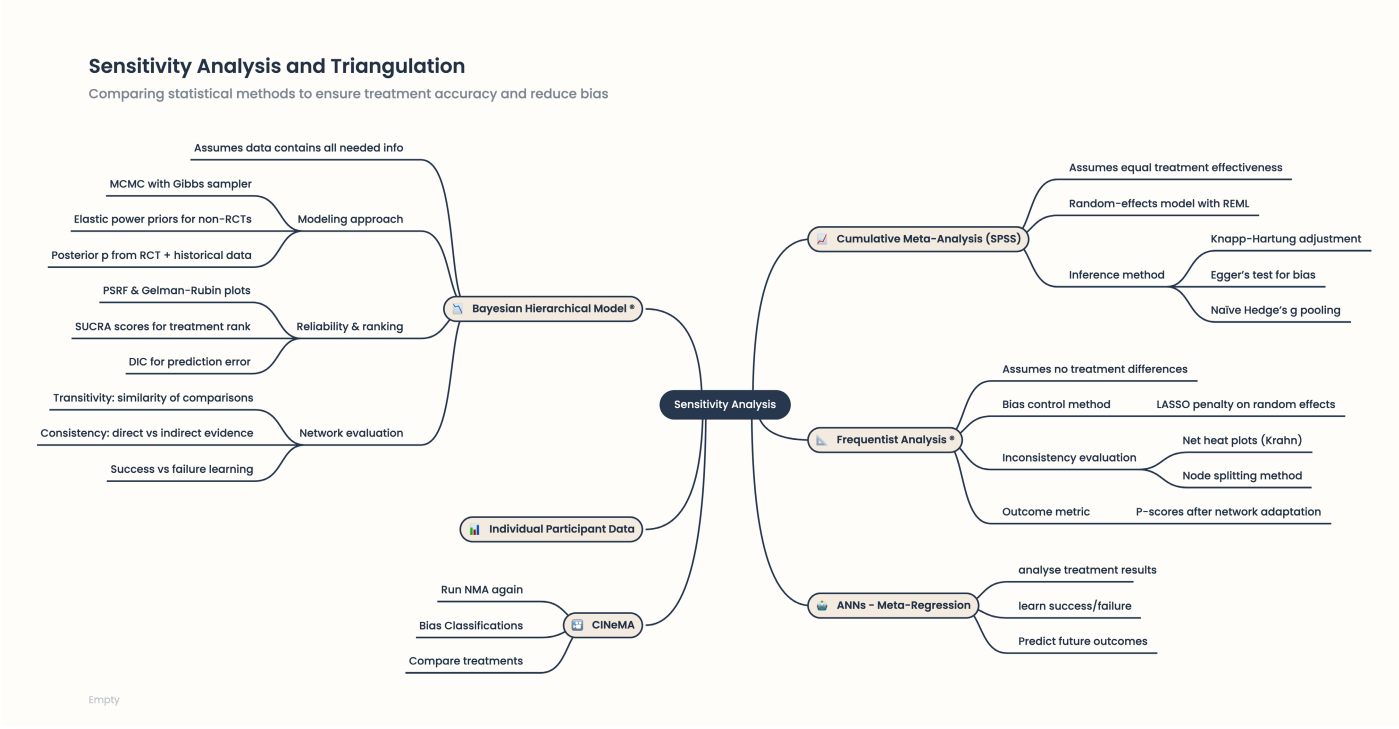


Diagram 1. Statistical analysis strategies used for this NMA graphically explained. Abbreviations: Artificial neural net (ANN), CINeMA=(Confidence in Network Meta-Analysis) DIC=(Bayesian Statistics), Deviance Information Criterion: IPD=individual participant data, LASSO= Least Absolute Shrinkage and Selection OperatorMCMC= Markov Chain Monte Carlo simulations, PSRF=Potential Scale Reduction Factor, SPSS=Statistical Package for the Social Sciences, SUCRA=Surface Under the Cumulative Ranking curve.

DISCUSSION

There is significant evidence that anorexia is affected by endocrinologic, metabolic, and genetic factors in addition to epigenetics. In studies were magnetic resonance imaging (MRI) and functional MRI (fMRI) scans were conducted, there were marked differences in brain structures and volumes of AN patients. Furthermore, blood, oxygen and glucose flows, as well as neurotransmitter uptakes were measurably different.[9]

Studies comparing the effects on the body of patients with AN and other anorexia types conclude that most patients are affected in the same major domains: metabolic; body weight/body composition (muscle, bone, adipose tissue), immune system, and neuropsychiatric. Patients with AN can be cachectic or sarcopenic and if not treated may die.[3] Altered levels of pro-inflammatory cytokines such as TNF-a, IL-6, and IL-1B have been identified in patients of all anorexia types and are considered as biomarker candidates.[21] A recent study by Himmerich et al[22] stresses the importance of biomarkers and therapeutic drug monitoring for Olanzapine levels in AN patients. The pharmacogenetics of Olanzapine and pharmacodynamics (P-450 CYP1A2/CYP2D6) are highlighted in the context of treatment response.[22]

Drug-induced weight gain is a well-studied ADR.[23] Numerous studies confirm that the MOA of each drug and many resulting ADRs depend on individual pharmacogenomic variations. These can be responsible for weight-gain, when some patients take specific drugs such as corticosteroids, synthetic hormones, cannabinoids, antipsychotics, antidepressants, antiepileptics, beta-blockers, or anti-diabetic drugs.[24]

Genomic loci associated with antipsychotic-induced weight gain, include genotypic and allelic frequencies of CNR1, rs1049353 and INSIG2, rs7566605, rs78310016, the genetic-epigenetic modulation of CRTC1 gene, the Met/Met genotype of BDNF Val66Met, Val/Val genotype, Val66Met-rs1519480 G/A haplotype, and Val66Met-rs11030101. Patients with these genetic variations gain weight when treated with certain types of antipsychotics, whilst others do not. The same applies to patients that are CYP2C19 poor or intermediate metabolizers who gain significantly more weight when prescribed the anti-depressant citalopram as opposed to patients who are fast metabolisers. Polymorphisms in HTR2C/759T/697C alleles, CNR1, leptin gene/2548A/G SNP, NPY, MC4R, ADRB3, and CYP2D6 are reported to induce weight-gain, when patients take Olanzapine.[25,26]

Genome-wide association studies, such GWAS and ANGI, indicate that AN is a result of genetic and epigenetics. Genetics can amount to as high as 84%.[27]

The role of gut microbiota in the genetics and pathogenesis of AN as well as other types of anorexia has been highlighted repeatedly. Body mass index/weight, in addition to other factors, affect the composition and ratios of specific gut bacteria and are important in the dysbiosis of some enterocytes. Altered firmicutes/bacteroidetes ratios have been consistently reported in anorectic and malnourished or cachectic patients following use of olanzapine or risperidone.[28] Olanzapine-induced dysbiosis of enterorhabdus, parasutterella, and prevotellaceae may induce weight gain.[29] Cyproheptadine and Mirtazapine are also reported to affect gut-bacteria, but research is still lacking.

Alterations in microbiota have been further linked to AN metabolic dysfunctions, including weight-gain, elevated triglycerides, changes in glycemic levels, and increased proinflammatory cytokine expression.[30]

Table 2. Anorexia Nervosa Treatment Ranking per Category, Network Meta-Analysis Algorithm

Treatment Category	*P-Score*	Intervention Type	*P*-Score per Treatment Intervention (Subgroup Analysis)
Surgically invasive neuromodulation DBS, capsulotomy (augmented with medications)	.00	Capsulotomy DBS	.00 .08
Pharmacological antipsychotics, antidepressants, cyproheptadine	.17	Olanzapine Cyproheptadine SSRIs, TCAs	.12 .26 .52
Non invasive neuromodulation rTMS, tDCS, ECT	.46	ECT tDCS rTMS	.28 .59 .66
Placebo/Sham treatments	.60		
Psychotherapies CBT-E, MANTRA, CRT, FT, psychotherapies	.61	CBT-E CRT MANTRA FT	.39 .51 .68 .98
Dietetic interventions	.74	Compulsory diet Voluntary diet	.65 .91
Specialist supportive clinical management	.93		

NMA Netranking of AN treatments in the Network. Smaller *P*-score indicates a more successful treatment. The 2 left columns show the *P*-scores per treatment category, whilst the 2 right columns show the *P*-scores for the subgroup analysis per individual treatment intervention. $Tau^2 = 0.0887$; tau = 0.2978; $I^2 = 56\%$ CI [42.4%; 66.3%]d.f. 61, *P*-value < .0001. CBT-E, cognitive behavioural therapy enhanced; CRT, cognitive remediation therapy; DBS, deep brain stimulation; ECT, electroshock treatment; FT, family therapy; MANTRA, the Maudsley Model of Anorexia Nervosa Treatment for Adult; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation. SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

The antipsychotic Olanzapine, which the NMA ranked as best performing from the pharmacological treatments, disrupts gut microbiota homeostasis, leading to a reduction in short-chain fatty acids. This reduction decreases serotonin secretion in the gut, which activates the orexigenic axis and alters the Neuropeptide Y (NPY)/agouti-related peptide (AGRP) ratio, contributing to lipid accumulation. Consequently, Olanzapine, like many other antipsychotics, promotes lipid biosynthesis through gene expression alterations.[31]

The NMA sub-group analysis indicated that Olanzapine and Cyproheptadine, from the pharmacological treatments, were superior to other drugs, with frequentist *P*-scores Olanzapine = 0.12 Cyproheptadine = 0.26 (smaller *P*-scores indicate better performance). Olanzapine had a network calculated effect size of 1.03 (0.78-1.27) 95% CI and Cyproheptadine of 0.48 (0.25-0.70) 95% CI. Bayesian SUCRA scores summarising NMA treatment rankings were Olanzapine = 0.89 and Cyproheptadine = 0.74 (higher SUCRA scores indicate greater probability of a treatment being superior). All statistical analyses agreed that patients treated with Olanzapine or Cyproheptadine had a higher chance for better treatment outcomes.

Ye et al,[32] in a systematic review of 6 RCTs of AN patients treated with Olanzapine, concluded that Olanzapine is an effective treatment for AN with an all-articles-pooled together weighted-mean difference (WMD) = 0.53. Subgroup analyses revealed that the increase in BMI was significantly higher in patients treated with a higher dose of Olanzapine (doses of 10 mg per day) with WMD = 1.38.[32] Another RCT, by Attia et al,[33] with psychiatric patients with anorexia and obsessive compulsive disorder (OCD) reported a 0.259% BMI increase weekly over 16 weeks, whilst a meta-analysis by Ruijun et al concluded that olanzapine resulted in an average 0.68% BMI increase.[34]

Cyproheptadine ranked as second-best performing from the pharmacological treatments. It is a first-generation anti-histamine (5-HT1A/5-HT2A antagonist), with anti-cholinergic and sedative effects. It has been investigated over many years, for the treatment of anorexia. It is clinically indicated in treating serotonin syndrome, high serotonin levels in autism, irritable bowel syndrome, functional gastro-intestinal symptoms, as schizophrenia treatment augmentation, in abdominal migraine with nausea/vomiting, in stimulant-induced appetite loss, in antidepressant-induced sexual dysfunction, allergies, headaches, and motion sickness.[36,37]

Kim et al[38] in a multicenter double-blinded RCT across 15 hospitals in Korea reported statistically significant weight changes in all patient groups, with non-significant side-effects. Cyproheptadine is approved as anorexia treatment in South Korea.

Capsulotomy and DBS ranked amongst the best performing for BMI/weight changes pre/post treatments, with cumulative SMD = 1.43(1.00-1.86) and *P*-scores capsulotomy = 0.00 and DBS = 0.0.8. These experimental, and perhaps controversial treatments, reported the longest follow-up and best BMI/Weight maintenance post-intervention. Anorexia nervosa subtypes were mixed, illness severity more serious, patients had multiple psychiatric comorbidities, were on multiple psychotropics and were mostly treatment resistant. Results were corroborated by psychiatric scales showing clinical improvement, discontinuation of drug treatments on some occasions, improvements in psychopathology and better quality-of-life outcomes. However, network-calculated effect sizes had wide CIs, and large error of effect sizes. These suggest uncertainty, and therefore further research is needed to explore their efficacy in clinical practice.

Hsu et al,[39] in a systematic review of DBS for eating disorders, concluded that DBS is effective for chronic AN patients. Overall, BMI increase was 24.82% in 17.1 months. The most common place for electrode insertion was reported as the subcallosal cingulate cortex (SCC) for 52% of patients, followed by Nucleus Accumbens (NAcc) for 33% of patients. Subcallosal cingulate cortex has also been identified as a therapeutic target in treatment-resistant depression. Deep brain stimulation downregulates activity in that area. Nucleus Accumbens together with the Anterior Limb of Internal Capsule, are loci of interest for OCD, whilst NAcc has also been targeted in depression, addiction and Tourette's.[39]

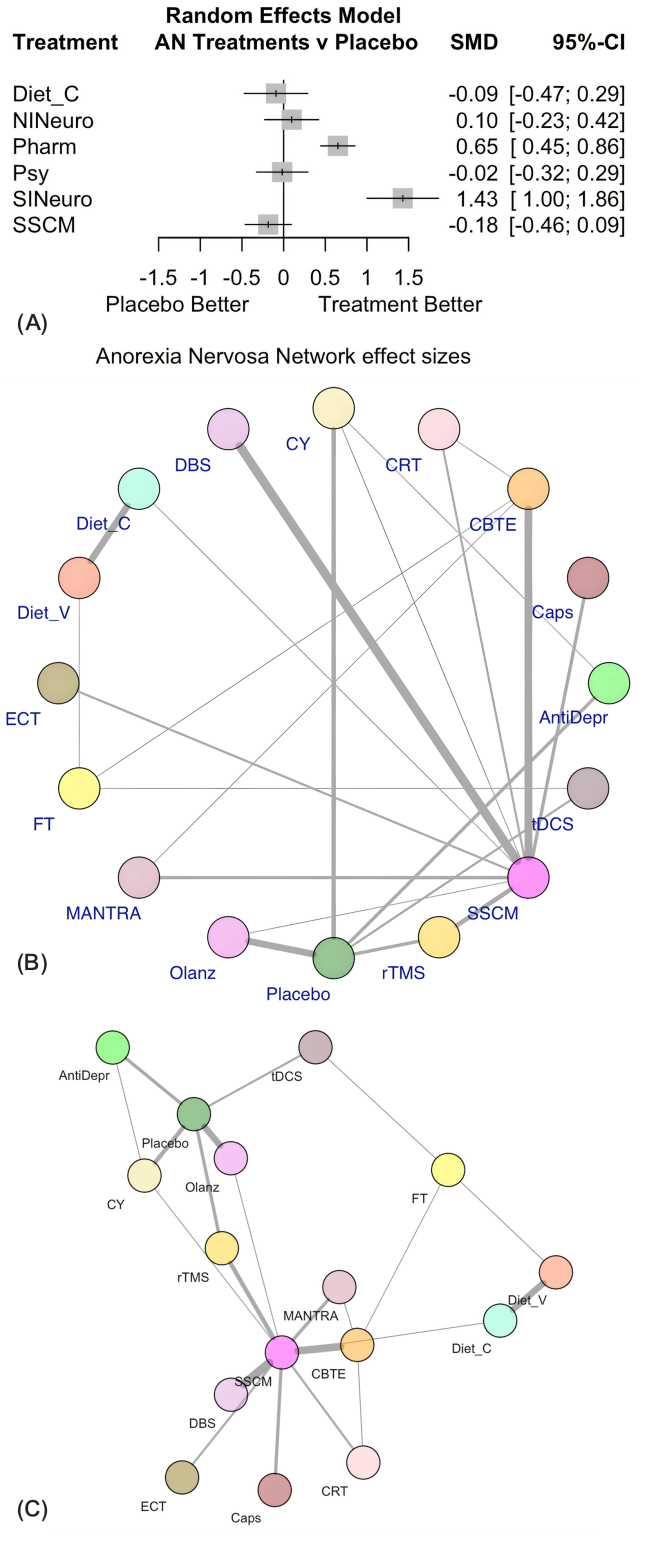


Figure 1. (A) Anorexia nervosa therapies. Random effect model, network calculated weighted pooled effect sizes per treatment category. In (B) Anorexia nervosa treatments network meta-analysis geometry by subgroup entire layout and in (C) by the Fruchterman-Reingold algorithm. Each treatment is represented by a different colour. The size of the spheres is symbolic and does not represent the weight of each study (to improve readability). The thickness of connections between treatments represents the strength of associations.

An open label DBS trial by Lipsman et al[40] for patients with refractory AN reported abnormalities in the cerebral glucose metabolism in the anterior cingulate, insula, and parietal lobe neurocircuitries. After 12 months of neurostimulation, a significant mean BMI improvement was noted. Patients were screened with PET scans before and after the trial. At the start of the trial, average BMI at DBS electrode insertion surgery was 13.83. Patients had comorbid mood disorders, anxiety disorders, or both. Mean BMI after 12 months of neurostimulation was 17.34. Significant improvements in measures of depression, anxiety, and affective regulation were reported. Mean Hamilton Depression Rating Scale scores were 19 at baseline vs. 9 at 12 months, whilst mean Beck Anxiety Inventory score at baseline was 38 vs. 27. Mean Dysfunction in Emotional Regulation Scale Score at baseline was 131 vs. 104 at 12 months. Patients were concurrently treated with antidepressants and antipsychotics.[40]

For non-invasive neuromodulation (rTMS, tDCS, ECT), cumulative SMD was 0.10 (–0.23-0.42) 95%CI, and subgroup analysis *P*-scores were ECT = 0.28, tDCS = 0.59, and rTMS = 0.66. Number of sessions, pulses, frequencies, and currents differed, although for rTMS and tDCS, almost all studies targeted the left dorsolateral prefrontal cortex (DLPFC). These treatments overall did not perform well, but treatment duration was shorter compared to other types and that can be significant for chronically ill patients. In the majority of those interventions, treatments were short-term varying from 1 session to 10 sessions on average.[41]

In the case of ECT, there were significant differences in administered treatments, in terms of duration, lateralization, and voltage.[42] Electroshock treatments were moderately successful as augmentation for anorectic patients with other comorbidities in acute phases, but the CI was wide and it was not possible to draw valid conclusions. It was noted that ECT augmentation appeared somehow more effective in older adults.[42]

An rTMS randomized controlled feasibility trial by Dalton et al, of 20 sessions to the left DLPFC (TIARA study), concluded that rTMS for AN can be effective in the long-run. This was a well-designed study with high patient retention rate, and 1-, 4-, and 18-month follow-ups.[43]

Bauman et al,[44] in an RCT with 43 AN patients undergoing 10 rTMS sessions of anodal tDCS over the left DLPFC, reported non-significant improvements in maladaptive eating behavior, BMI, and depression. However, patient retention rate was higher compared with other studies.[44]

Network meta-analysis SMD for all psychotherapies was –0.02 (–0.32-0.29). Subgroup analysis ranked CBT-E as best performing compared to other psychotherapy types, with *P*-score = .39. The *P*-scores for CRT = 0.51, MANTRA = 0.68 and FT = 0.98, indicate that they did not perform well. Imaging studies show that CBT affects brain neuroplasticity, which may explain partly, why it performed best.[45] Network meta-analysis results suggest that psychotherapies performed worse than other therapeutic interventions. Patients with low BMI have memory, cognition, and thinking deficits. It can be difficult to respond to psychotherapy under those circumstances.[22]

Fairburn et al, discussed CBT-E for AN patients that was focused on helping patients change their behavioral patterns and improve in terms of eating psychopathology. BMI increase was reported to be 1.80 kg/m^2 and eating disorder psychopathology was reported as improved. At 60-week follow-up, residual eating disorder psychopathology

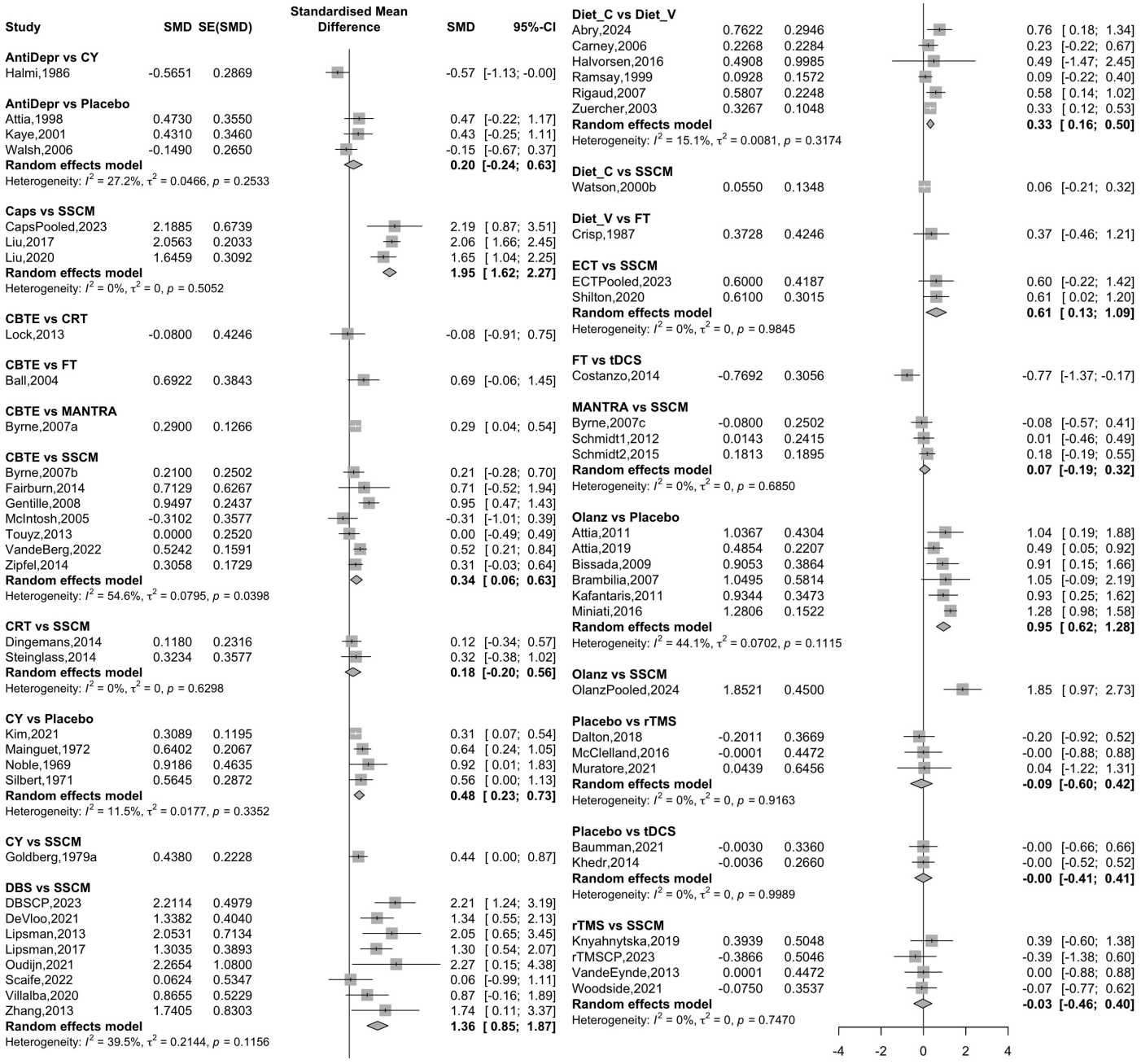


Figure 2. Studies included in the anorexia nervosa network. Random effects model. Standard mean difference for each study, standard mean difference error, heterogeneity per treatment type, 2 and probability for each comparison, with 95% CI. Results are grouped per intervention type and comparisons as performed by the network.

decreased from 87% (55/63) to 78% (43/55) and the percentage of patients with a BMI ≥ 18.5 reduced from 62% (39/63) to 55% (30/55).[46]

The MOSAIC Study in the UK was a multicenter RCT trial that compared MANTRA vs. SSCM. Mean BMI increases measured at end-of-treatment were 1.75 kg/m^2 for MANTRA and 1.36 kg/m^2 for SSCM. Body mass index increased by 2.25 kg/m^2 and 2.16 kg/m^2 at 24-months post-randomization follow-up. Subsequent comparisons of MANTRA results fail to confirm efficacy. Solmi et al,[45] in an NMA published in the Lancet, cannot confirm the effectiveness of the MANTRA intervention and Van den Berg et al,[47] in a meta-analysis of psychological treatments, report effect-sizes for MANTRA hedges g = −0.95, p = 0.00, which suggest that the MANTRA intervention performs worse than others in real-life clinical settings.

The ANTOP trial compared treatment efficiency for FPT and CBT-E vs. optimized treatment-as-usual (TAU or else SSCM). The study reported BMI increases at treatment-end for FPT = 0.73 kg/m^2, CBT-E = 0.93 kg/m^2 and TAU = 0.69 kg/m^2. The conclusion was that CBT-E is better than other treatments, but earlier interventions are needed. A 5-year follow-up of the ANTOP trial report an overall poor global outcome and no major BMI changes.[48]

Compulsory, voluntary and NG tube feeding therapies did not perform well, and weight was not maintained post-treatment, with

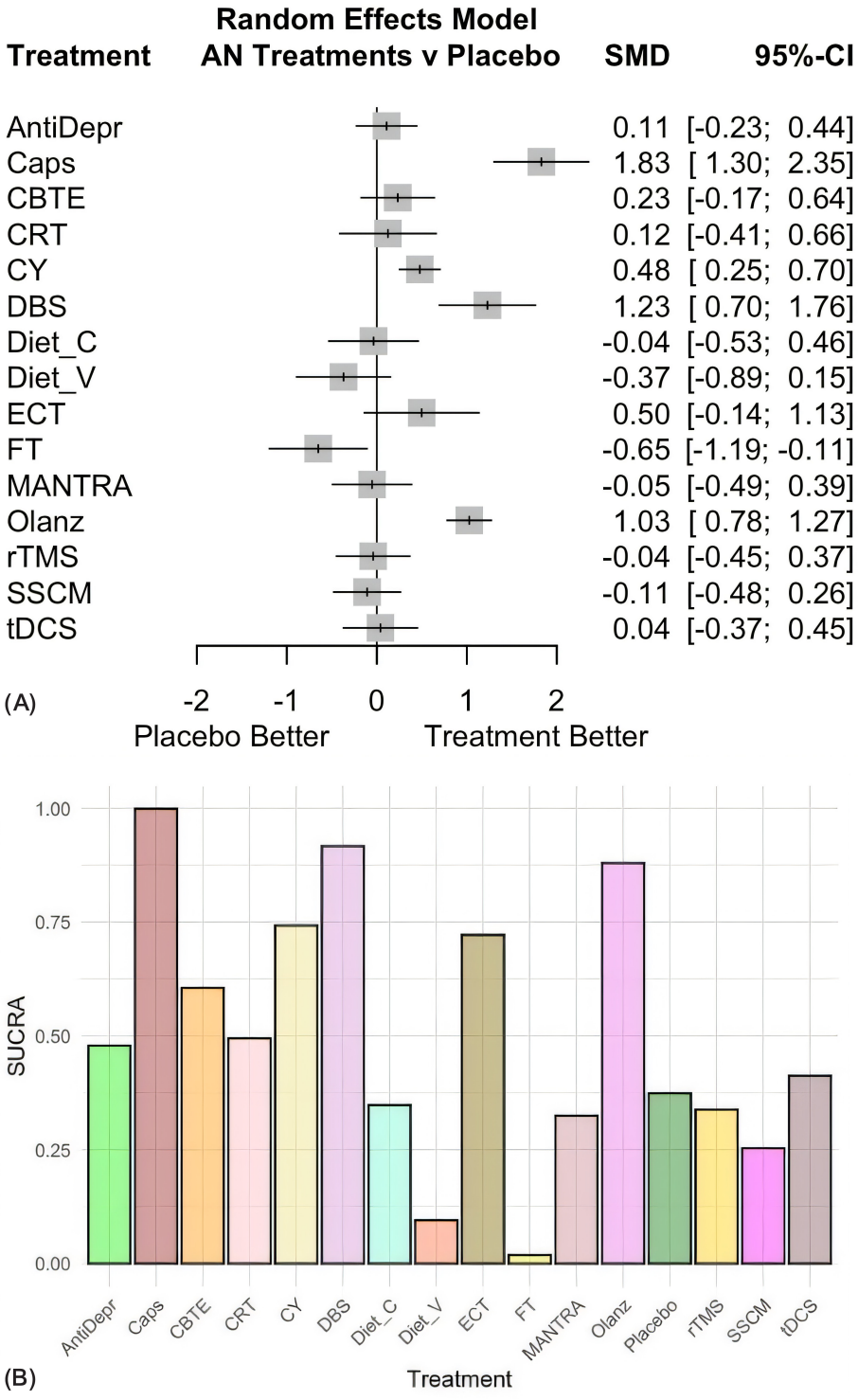


Figure 3. (A) Anorexia nervosa treatment standardized mean differences with regards to BMI or weight change, relative to placebo. Network effect sizes. The non-RCT network is penalized by power prior P=.5. (B) anorexia nervosa treatments, SUCRA scores (Bayesian analysis).

patients having multiple readmissions. Network meta-analysis SMD was −0.09 (−0.47-0.29) and compulsory diets *P*-scores were .65 (better than voluntary diet *P*-scores = .91).[8]

Specialist supportive clinical management had the lowest NMA SMD = −0.18 (−0.46-0.09) and ranked as one of the 3 worst-performing treatments, along with compulsory diets and psychotherapies.

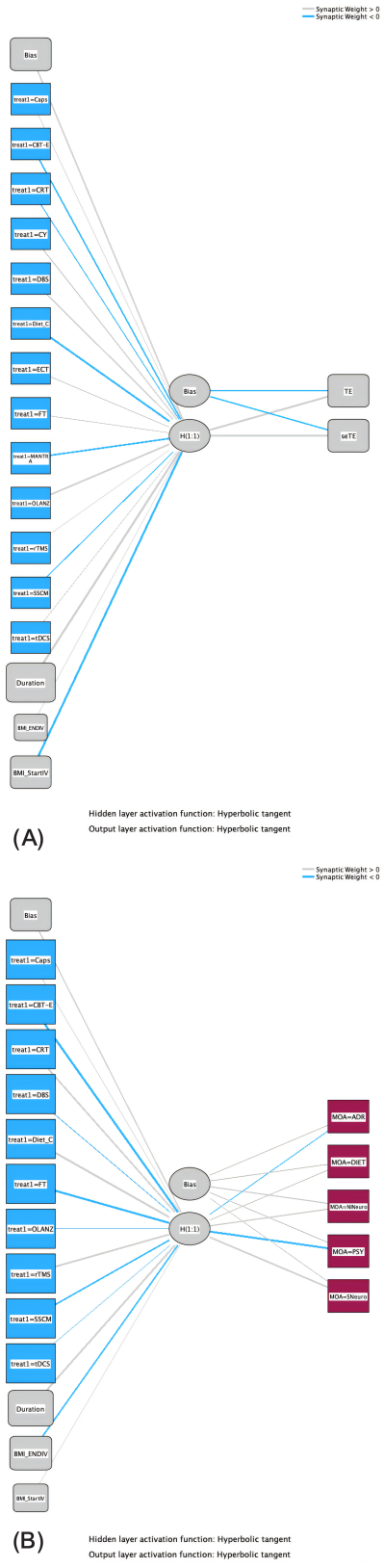


Figure 4. (A) Anorexia nervosa. Multi-layer perceptron, meta-regression with covariates—duration of treatment in weeks, intervention starting (BMI_StartIV) and ending BMI (BMI_EndIV). Factors are treatment interventions and outputs are effect size TE and standard error of effect size (seTE). The thickness of interconnecting lines represent the significance of synaptic weights, the color blue is for synaptic weights < 0, whilst the color gray is for synaptic weights > 0. Synaptic weights govern transformation and information propagation through the ANN, by adjusting the weights, so the ANN learns patterns and performs various tasks (regression, classification, prediction). (B) Anorexia nervosa. Multi-layer perceptron, classification with covariates in weeks, and starting and ending BMI as covariates. Covariates are effect size TE, standard error of effect size seTE. Factors are individual treatments. Output is the Mode of Action of treatments (MOA) with 4 main classifications: ADR, Diet, NINEURO(non-invasive neuromodulation), SNeuro(surgically invasive neuromodulation), PSY(psychotherapies).

Most studies highlighted the non-standardisation of patient inclusion criteria, treatment plans and reporting. Most studies, included mixed AN subtypes and severities. There were no within-study customized therapeutic plans for different subtypes. In some cases, psychiatric comorbidities, and drug treatments, were not discussed.[8] A systematic review of 6747 AN patients from the Danish national register, revealed extensive polypharmacy with psychotropics, ECT treatments, multiple psychiatric comorbidities and inconsistent patient management with spurious psychotherapeutic support.[49]

Comparing treatment interventions was a challenging task, due to uncertainty, variability, reporting inconsistency, and treatment type overlap. Particularly challenging, were the comparisons of surgical neuromodulations with psychotherapies and pharmacotherapies. There were no RCTs, no standardisation of capsulotomy techniques, or of DBS electrode insertion sites, frequencies, durations and number of sessions. Patients were opportunistically sampled, often severe/treatment-resistant cases with comorbidities, on long-term polypharmacy, and psychotherapy. It was thus difficult to compare them against other treatment interventions that included patients representing a larger population of interest, with less severe AN subtypes and had different selection criteria. Furthermore, there are numerous ethical considerations, as these experimental treatments are surgically invasive, and many researchers agree that it is morally ambiguous to enrol patients in RCTs where sham surgeries are involved.

These NMA results should be interpreted with caution. The mixed disease severity, subtype heterogeneity (AN-R, AN-BP, SE-AN, AN-unspecified), and comorbidities, can be confounding variables, affecting both interventions and outcomes. Patients may respond differently to a particular intervention, increasing result heterogeneity and skewing treatment effect sizes, reducing thus confidence in findings. Analysis per AN subtype with/without comorbidities, was inconclusive due to the above. The probability that patients improved, because the comorbidity was treated, should also be taken into consideration. The grouping of treatments and combination of result, can also be considered another confounder. There are many parameters for consideration due to study variability and individual differences. That necessitated extensive sensitivity analyses and multiple-checkpoints to verify NMA outcomes. Indeed, over half of the studies were excluded at that stage (55/118). The final NMA study heterogeneity was however within acceptable limits, increasing thus confidence in estimations.

The neural net meta-regression was designed to simultaneously test multiple study characteristics as input factors (see study coding in methods) and to train ANNs on historic patient data. Artificial neural

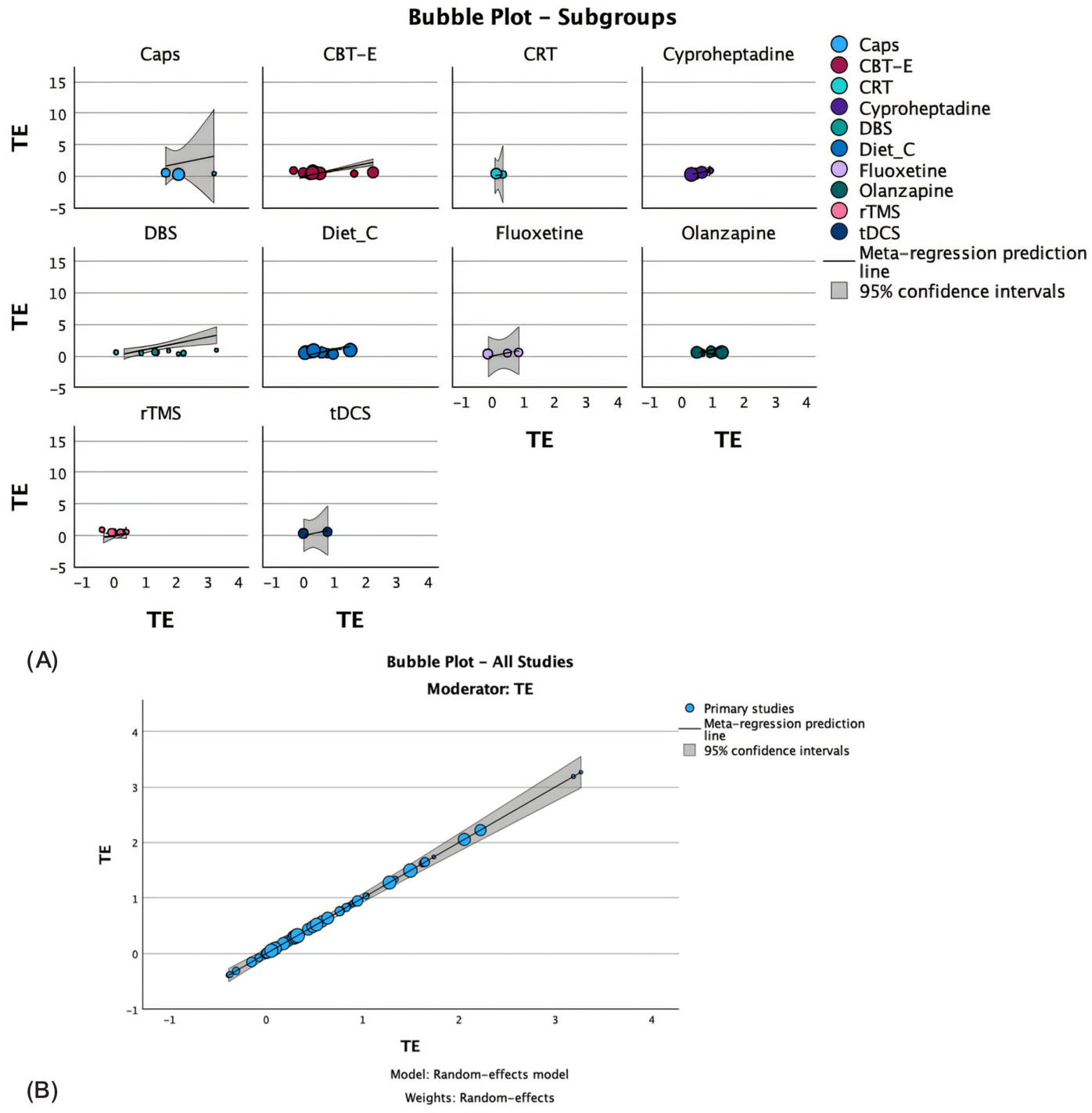


Figure 5. (A) Meta-regression predictions of treatment efficiency based on treatment effect size (TE). Analysis shown per treatment type. (Note that the network has rejected ECT, due to insufficient number of studies in the meta-regression), and for all primary studies together (B).

nets are more suitable to process mixed illness severity data, as they capture complex non-linear relationships. The main disadvantage was the relatively small number of analysed studies and patients. Large ANNs predict significantly better when trained with many thousands/millions of cases. The dataset size constrained us in the use of more appropriate ANN models such as graph, recurrent or convolutional neural networks, used in causal machine learning.[50]

The most appropriate model for the authors' dataset was the multilayer perceptron.

Artificial neural nets explored which study-level characteristics affected treatment outcomes from the historic data (all factors tested), by "learning" success/failure (from effect size, error of effect size). Based on these learnt patterns, they were able to

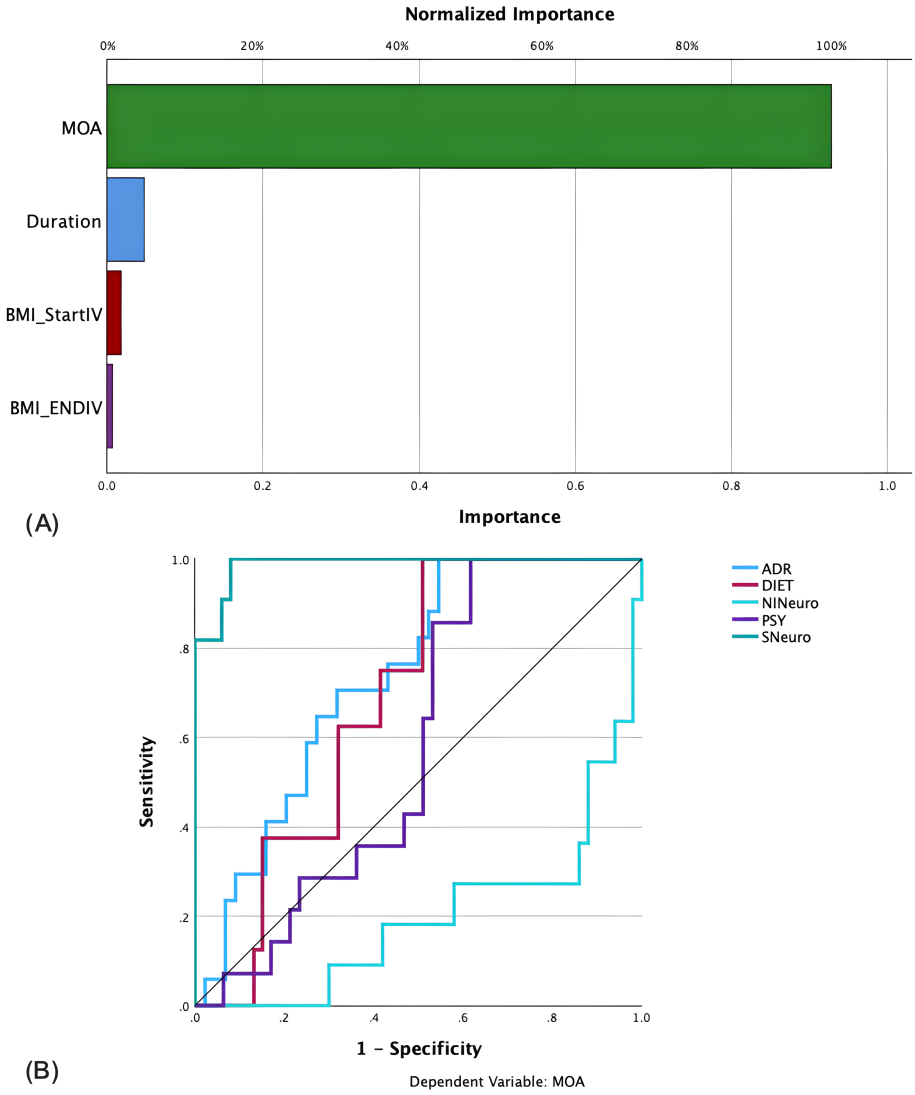


Figure 6. (A) Meta-regression runs with multi-layer perceptron, factor importance testing. The mode of action (MOA) of treatments, as well as treatment duration (in weeks), were the 2 most important factors in predicting treatment success, followed by the intervention starting BMI (BMI_StartIV) as well as the intervention ending BMI (BMI_ENDIV). (B) Sensitivity and Specificity for the MOA as determined by the ANN with MOA=ADR 0.737, SNeuro=0.987, Diet=0.686, NINeuro=0.200, PSY=0.581.

predict which factors have higher chances of affecting intervention outcomes. Artificial neural nets identified the MOA of the treatment that resulted or not, in an ADR (weight-gain yes/no), as the factor that is most likely to affect future treatment outcomes. The treatment whose MOA resulted in most successful treatment outcomes by causing the desired ADR (weight change) was the drug Olanzapine. Other factors such as treatment duration, before/after treatment BMI/weights were estimated as less important.

In the context of recent pharmacogenomic and gut-bacteria research, ANN findings suggest that Olanzapine has higher chances of affecting future treatment outcomes. There is extensive evidence that drugs like Olanzapine, interact with specific genes and processes that affect body weight. This does not necessarily mean that Olanzapine is the panacea for AN. Response to a drug is highly dependent on individual pharmacogenetic profiles. The mechanisms by which drugs affect gene expression and gut-microbiota symbiosis in AN patients, need to be investigated further with pharmacogenomic testing.

Our findings must be interpreted with caution due to the many limitations of this research. However, the authors aspire to highlight the importance of pharmacogenomic testing, precision medicine and the use of artificial intelligence in identifying appropriate treatments and predicting their efficacy in clinical practice.

CONCLUSION

Anorexia mechanisms are highly complex and not completely understood. The neurochemical pathways involved have yet to be precisely defined. Pharmacogenomic profiling is increasingly shown to be significant in identifying targeted, individualized and effective treatments. Additional research is necessary to determine which genetic variations can be used to inform new treatments. The vast majority of current interventions for AN, are off-label and depend on adverse

drug reactions. The authors' findings suggest that drug repositioning for Olanzapine and Cyproheptadine should be explored further. Precision medicine treatments, specifically tailored to the pharmacogenomic profiles of AN patients, should be prioritized.

Artificial Intelligence when used in the analysis and prediction of treatment efficacy, can capture complex non-linear relationships and reveal factors that have higher chances of affecting treatment outcomes, in the real-world. In this way, the authors can inform clinical practice, enhance patient safety and guide targeted drug development.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K.; Design - S.K.; Supervision - F.B.V., A.M.; Resources - S.K., I.C.P.; Materials - S.K., I.C.P.; Data Collection and/or Processing - S.K., I.C.P.; Analysis and/or Interpretation - S.K., F.B.V., I.C.P., A.M.; Literature Search - S.K., F.B.V., I.C.P., A.M.; Writing Manuscript - S.K., I.C.P.; Critical Review - F.B.V., A.M.; Other - P.M.A., J.A.

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