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Title: Efficacy and Safety of Pharmacotherapy in Cancer-Related Anorexia and Cachexia Symptoms: An Updated Systematic Review and Network Meta-Analysis

Running Title: Meta-analysis in Treatment of cancer-related anorexia and cachexia

Authors: Ashlynn Brar[1], Noah Kim[1], Pankaj Soni[1], Kush Shah[2], Jyoti Bajpai[3]

[1] Department of Critical Care, EMC Super Specialty Hospital, Amritsar, Punjab, India

[2] Department of Surgical Oncology, KD Hospital, Ahmedabad, India

[3] Medical and Precision Oncology, Apollo Hospitals, Chennai, India

Correspondence: Pankaj Soni

Address: Backside Income Tax office, Green Avenue, Amritsar, Punjab 143001, India

Department of Critical Care, EMC Super Specialty Hospital

Tel: +91 7009182189

Email: drsonipankaj@rediffmail.com

Clinical Question Box

Is pharmacological treatment suggested for Cancer-Associated Anorexia and Cachexia?

Pharmacological treatment is moderately supported for Cancer-Associated Anorexia and Cachexia Syndrome. Olanzapine is effective for weight gain and improving the anorexia-cachexia subscore, with a favorable safety profile. Anamorelin and ponsegromab show promise as emerging options. In contrast, mirtazapine has limited efficacy and a higher risk of serious adverse events, making it less suitable.

Abstract

Introduction: Cancer-associated cachexia syndrome (CACS) is a complex condition characterized by anorexia, weight loss, and muscle wasting, significantly affecting quality of life and treatment outcomes. The comparative efficacy and safety of pharmacological treatments remain uncertain.

Methods: A systematic review and network meta-analysis were conducted using randomized clinical trials (RCTs). Three databases were searched for studies published between 2000 and 2024. The analyzed outcomes included absolute weight gain, improvement in the anorexia-cachexia subscore (ACS), and the risk of serious adverse events (AEs).

Results: Nine studies involving 1,505 participants were analyzed. Olanzapine demonstrated the most significant weight gain (MD 4.6 kg, 95% CI: 0.82–8.38), while ponsegromab 400 mg and anamorelin 100 mg were effective in maintaining weight, with gains of 3.26 kg (95% CI: 2.35–4.17) and 2.38 kg (95% CI: 1.82–2.94), respectively. However, the network meta-analysis did not confirm the superiority of olanzapine over ponsegromab or anamorelin. Mirtazapine showed limited benefits in weight gain. Regarding ACS, olanzapine demonstrated the highest efficacy, with significant improvement compared to ponsegromab 400 mg (MD 6.5, 95% CI: 1.3–11.7), anamorelin 100 mg (MD 6.9, 95% CI: 1.6–12.1), mirtazapine 15 mg (MD 10.0, 95% CI: 5.8–14.2), ponsegromab 200 mg (MD 10.3, 95% CI: 6.1–14.5), and anamorelin 50 mg (MD 10.3, 95% CI: 5.1–15.4), confirming its superior ACS improvement through network meta-analysis. All but mirtazapine showed acceptable safety profiles, with serious AEs (odds ratio: 5.93, 95% CI: 2.35–14.96). Only mirtazapine showed an increased risk of serious AEs with an odds ratio of 5.93 (95% CI: 2.35–14.96).

Conclusions: Olanzapine demonstrated notable benefits in weight gain and ACS improvement with a favorable safety profile while emerging agents like anamorelin and ponsegromab show promise in managing CACS.

Keywords: cancer-associated cachexia syndrome, anamorelin, olanzapine, mirtazapine, ponsegromab, meta-analysis

Introduction

Cancer-related anorexia-cachexia syndrome (CACS) is a complex condition marked by a persistent lack of appetite and progressive body weight loss, often accompanied by significant reductions in both muscle mass and adipose tissue.[1] The prevalence of anorexia-cachexia varies depending on the type of cancer, affecting approximately 80% of patients with pancreatic or gastric malignancies, 54–60% of those with lung, prostate, or colorectal cancers, and 32–48% of individuals with breast cancer, sarcoma, lymphoma, or leukemia.[2] Beyond its impact on physical health, CACS profoundly diminishes the quality of life (QOL), hampers the effectiveness of cancer therapies, leads to increased hospital admissions, and is implicated in nearly 20% of cancer-related fatalities.[3] Management strategies for CACS encompass a multidisciplinary approach, including nutritional guidance, tailored physical activity programs, and pharmacological interventions aimed at enhancing appetite, facilitating weight gain, and addressing metabolic abnormalities.[4]

Pharmacological treatment for CACS has advanced significantly, reflecting a growing understanding of its complex pathophysiology. CACS involves multifactorial mechanisms, including systemic inflammation, metabolic dysregulation, and altered appetite signaling.[5] Consequently, pharmacological interventions target various pathways to alleviate symptoms and improve patient outcomes. Progestogens, particularly megestrol acetate, have an extended treatment history and effectively stimulate appetite and promote weight gain, albeit primarily through fat accumulation rather than muscle preservation.[6] Despite their efficacy, side effects such as fluid retention and thromboembolic risks limit their use in certain patients.[7] Corticosteroids, such as dexamethasone, are widely employed for their appetite-stimulating and anti-inflammatory

properties. However, their benefits are typically short-lived, and adverse effects, including muscle wasting and immunosuppression, constrain prolonged use.[8]

Emerging therapies for CACS have introduced innovative strategies targeting key physiological mechanisms to address its multifaceted challenges. Anamorelin, a ghrelin receptor agonist, exemplifies the promise of ghrelin analogs by mimicking the appetite-stimulating hormone to enhance food intake and preserve lean body mass with minimal adverse effects.[9] Meanwhile, olanzapine and mirtazapine, traditionally used as psychotropic agents, have shown potential as cytokine inhibitors by modulating pro-inflammatory pathways, such as those involving IL-6 and TNF-α, thereby mitigating muscle degradation and metabolic disturbances.[10,11] Ponsegromab, a humanized monoclonal antibody inhibiting growth differentiation factor 15 (GDF-15), has been associated with improved weight, appetite, physical activity, and suppressed serum GDF-15 levels.[12]

These emerging therapies mark significant progress in addressing CACS by targeting distinct mechanisms of action—stimulating appetite, mitigating inflammation, and promoting muscle anabolism. Despite these advancements, notable challenges remain, including the scarcity of robust long-term efficacy data, variability in patient responses due to heterogeneity, and the complexity of tailoring treatments to individual needs. These limitations highlight the critical need for ongoing research into multimodal interventions that integrate pharmacological, nutritional, and rehabilitative strategies. This network meta-analysis synthesizes data from recent randomized controlled trials (RCTs) to evaluate the comparative efficacy and safety profiles of these therapeutic options. By providing a comprehensive and evidence-based framework, the analysis

aims to refine clinical decision-making, enhance individualized treatment planning, and ultimately improve QOL and clinical outcomes for patients with CACS.

Methods

Study Protocol

This network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] The protocol for this study was registered in the Open Science Framework to ensure transparency and methodological rigor.[14] This analysis is based solely on previously published data, so approval from an institutional review board was not required.

Data Search

Relevant studies were systematically identified through extensive searches of PubMed, Cochrane Library, and Web of Science databases, spanning January 1, 2000, to December 31, 2024. The search strategy employed terms addressing the condition and patient population ("cachexia" or "anorexia" and "cancer"), the interventions of interest ("treatment," "pharmacotherapy," or "therapy"), and the comparison group ("placebo"), ensuring a thorough selection of potential articles.

Eligibility Criteria

This network meta-analysis included RCTs that evaluated pharmacological interventions for cancer-related weight loss or anorexia in adults. Studies were eligible if they met the following criteria: (1) included adult patients diagnosed with CACS, (2) compared a pharmacological intervention with a placebo, and (3) reported relevant outcomes related to efficacy and safety. The exclusion criteria were as follows: (1) a sample size of fewer than 30 participants in all study arms,

(2) outcomes assessed within a duration of one month, (3) pharmacotherapy combined with supplementary interventions, and (4) studies focusing solely on supplementary interventions.

Data Extraction and Synthesis

Two reviewers (A.B. and N.K.) independently screened the titles and abstracts of identified studies, followed by a detailed full-text review to determine eligibility. Any discrepancies that could not be resolved through discussion were referred to a third reviewer (P.S.) for resolution. Data extraction was performed independently by two reviewers using a standardized form, capturing details on study characteristics, interventions, outcomes, and follow-up periods. Extracted data included participant demographics, cancer types, inclusion criteria, intervention specifics, and reported outcomes. No language restrictions were applied, allowing for the inclusion of studies from a broad range of sources. Furthermore, the reference lists of relevant articles were reviewed to ensure a comprehensive and expanded scope of the research.

Outcomes

Most studies did not report fat mass, lean body mass, and body mass index. The primary outcome was absolute weight gain. The secondary outcomes included the Anorexia/Cachexia Subscale (ACS) of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire and serious adverse events (AEs). The criteria for AEs were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0;[15] however, using a previous version was also acceptable due to the study period.

Statistical Analysis

Network meta-analysis was conducted using R software (Version 4.4, New Zealand) with the "meta" and "netmeta" packages, employing a random-effects model to account for variability between studies. The primary outcomes included mean differences (MDs) for continuous data, such as weight gain and ACS, and odds ratios (ORs) for dichotomous data, including the incidence of serious AEs. Results were reported with 95% Confidence Intervals (CIs) to indicate the precision of the estimates. The I^2 statistic was utilized to assess heterogeneity, with values of 0–25% indicating low heterogeneity, 25–50% representing moderate heterogeneity, 50–75% reflecting substantial heterogeneity, and >75% signifying considerable heterogeneity.[16] Detected inconsistencies were further examined through sensitivity analyses to identify potential sources of heterogeneity. Treatment rankings were determined using surface under the cumulative ranking curve (SUCRA) values, which provide a probabilistic assessment of the efficacy and safety of each intervention. Statistical significance was defined as a two-tailed p-value < 0.05.

Bias and Evidence-level

The Risk of Bias tool evaluated potential biases related to randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.[17] Based on these criteria, studies were categorized as having low risk, some concerns, or a high risk of bias. The overall confidence in the findings of each study was considered during the synthesis. Publication bias was assessed using funnel plots and followed by the Egger test. The quality of evidence was further appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[18]

Results

Data Search and Characteristics of Included Studies

Database searches identified 1,174 articles. After duplicate removal, initial screening, and secondary screening, 247, 860, and 57 studies were excluded, respectively, leaving 10 articles for the final review (Figure S1). However, one study comparing the efficacy of mirtazapine with megestrol acetate (160 mg daily) was ultimately excluded.[19] This exclusion was necessary because a network meta-analysis was not feasible, as no studies assessed the effect of megestrol acetate (160 mg daily) as a reference.

Nine studies, including a total of 1,505 participants, were analyzed.[20-28] These consisted of two anamorelin studies, two mirtazapine studies, and one study each on enobosarm, espindolol, olanzapine, pentoxifylline, and ponsegromab (Table 1). The studies varied in population characteristics, intervention types, and cancer types. Due to the lack of consensus on diagnostic criteria for CACS, the inclusion criteria across the studies differed. Three studies investigated pharmacotherapy for non-small cell lung cancer, while the remaining studies assessed treatments in either a multi-cancer setting or among patients without specified cancer types. Most studies evaluated outcomes over two to four months, with only one study extending follow-up to six months.

Absolute Weight Gain

Nine studies evaluated absolute weight gain, with the network graph presented in Figure S2. Direct comparisons indicated that olanzapine 2.5 mg daily resulted in the highest weight gain, with an MD of 4.6 kg (95% CI: 0.82 to 8.38). This was followed by espindolol 20 mg daily (MD 3.82 kg, 95% CI: 0.72 to 6.92), ponsegromab 400 mg daily (MD 3.26 kg, 95% CI: 2.35 to 4.17),

anamorelin 100 mg daily (MD 2.38 kg, 95% CI: 1.82 to 2.94), ponsegromab 200 mg daily (MD 2.37 kg, 95% CI: 1.50 to 3.24), ponsegromab 100 mg daily (MD 1.67 kg, 95% CI: 0.82 to 2.52), and anamorelin 50 mg daily (MD 1.32 kg, 95% CI: 3.652.50 to 2.23). All these treatments showed statistically significant differences compared to placebo (Figure 1A). In contrast, mirtazapine 15 mg daily did not demonstrate a significant benefit in weight gain.

The ranking of treatments based on 1,000 simulations is shown in Figure S3. Olanzapine 2.5 mg achieved the highest SUCRA value of 0.901, followed by espindolol 20 mg (0.855), ponsegromab 400 mg (0.845), anamorelin 100 mg (0.681), and ponsegromab 200 mg (0.676). The complete network meta-analysis is detailed in Table S1, while a summary is presented in Table 2. When comparing olanzapine 2.5 mg daily to ponsegromab 400 mg, anamorelin 100 mg, ponsegromab 200 mg, and anamorelin 50 mg, no significant weight gain differences were observed. The respective MDs were: 1.34 kg (95% CI: -2.6 to 6.0), 2.22 kg (95% CI: -1.6 to 6.1), 2.23 kg (95% CI: -1.7 to 6.1), 2.93 kg (95% CI: -0.9 to 6.8), and 3.28 kg (95% CI: -0.6 to 8.6).

Improvement in ACS

Six studies, including 1,174 patients, assessed ACS improvement; the network graph of these studies is shown in Figure S4. Direct comparisons revealed that olanzapine 2.5 mg daily resulted in the highest ACS improvement, with a mean difference (MD) of 11.0 (95% CI: 6.92 to 15.08), followed by enobosarm 1 mg daily, ponsegromab 400 mg daily, anamorelin 100 mg daily, ponsegromab 100 mg daily, and mirtazapine 15 mg daily, all of which demonstrated statistically significant differences compared to placebo (Figure 1B). In contrast, ponsegromab 200 mg and anamorelin 100 mg did not show statistically significant differences.

Figure S5 shows the treatment ranking based on 1,000 simulations. Olanzapine 2.5 mg achieved the highest SUCRA value of 0.997, followed by ponsegromab 400 mg (0.743), enobosarm 1 mg (0.735), ponsegromab 100 mg (0.708), and mirtazapine 15 mg (0.338). The complete network meta-analysis is provided in Table 3. Olanzapine 2.5 mg daily demonstrated superior ACS improvement compared to ponsegromab 400 mg, anamorelin 100 mg, mirtazapine 15 mg, ponsegromab 200 mg, and anamorelin 100 mg, with MDs of 6.5 (95% CI: 1.3 to 11.7), 6.9 (95% CI: 1.6 to 12.1), 10.0 (95% CI: 5.8 to 14.2), 10.3 (95% CI: 6.1 to 14.5), and 10.3 (95% CI: 5.1 to 15.4), respectively.

Serious AEs

Eight studies, including 1,441 patients, assessed serious AEs; the network graph of these studies is shown in Figure S6. Direct comparisons revealed that mirtazapine 15 mg daily was associated with an increased risk of serious AEs, with an OR of 5.93 (95% CI: 2.35 to 14.96). In contrast, no other agents demonstrated a statistically significant increase in serious AEs (Figure 1C). Figure S7 shows the treatment ranking based on 1,000 simulations. Enobosarm 1 mg had the lowest risk of serious AEs, followed by enobosarm 3 mg, ponsegromab 200 mg, olanzapine 2.5 mg, anamorelin 100 mg, and anamorelin 50 mg, with SUCRA values of 0.843, 0.739, 0.829, 0.719, 0.640, and 0.574, respectively. The summary of the risk of serious AEs was presented in Table 4, while the complete network meta-analysis results were detailed in Table S2. Ponsegromab 200 mg and anamorelin 100 mg were associated with a lower risk of serious AEs, with ORs of 0.18 (95% CI: 0.05 to 0.63) and 0.23 (95% CI: 0.05 to 0.97), respectively.

Risk and evidence level

The total I^2 values for weight gain, improvement in ACS, and serious AEs were 45.5% ($p = 0.16$), 0%, and 46.9% ($p = 0.15$), respectively, indicating low to moderate heterogeneity. The I^2 values for between-design heterogeneity were 51.9% ($p = 0.15$), 0%, and 71.9% ($p = 0.06$), respectively, particularly for serious AEs. A sensitivity analysis was performed by excluding the study by Arrieta 2024 from the serious AEs analysis. This exclusion resulted in a substantial reduction in heterogeneity, with the I^2 dropping to 0% for both overall and between-design heterogeneity. Importantly, despite this change in heterogeneity, the ranking of AEs remained unchanged, reinforcing the robustness of the findings (Figure S8, S9). The risk of bias is shown in Figure S10. Three studies evaluated the efficacy of the agents over a two-month period, which was deemed inadequate follow-up, resulting in a high risk of bias[20,24,25] Two additional studies displayed selection bias due to small sample sizes or ambiguous diagnostic criteria[26,27] No significant publication bias was detected. The p-values from Egger's test for the outcomes of weight gain, improvement in ACS, and serious AEs were 0.06, 0.22, and 0.11, respectively. According to the GRADE approach, the evidence showed moderate certainty for outcomes such as weight gain, improvement in ACS, and the incidence of serious AEs.

Discussion

This meta-analysis evaluated the efficacy and safety of pharmacological interventions for CACS, focusing on various agents. Olanzapine demonstrated notable efficacy in promoting weight gain, comparable to ponsegromab and anamorelin, although mirtazapine appeared less effective. However, the network meta-analysis did not establish olanzapine as superior to other agents for weight gain. This finding contrasts with the results of a previous network meta-analysis.[29] For improving ACS, olanzapine, ponsegromab, and mirtazapine showed effectiveness, whereas anamorelin did not. The network meta-analysis highlighted olanzapine as a higher-priority option than ponsegromab, mirtazapine, and anamorelin for ACS improvement. Safety profiles varied, with mirtazapine associated with a higher incidence of serious adverse events, while most other treatments did not raise significant safety concerns. This analysis provides a comparative perspective on these interventions, emphasizing the potential role of olanzapine in managing CACS.

The findings of this analysis have significant clinical implications for the management of CACS, a debilitating condition with limited treatment options. Olanzapine, a medication traditionally used for psychiatric conditions, demonstrated a dual benefit by promoting weight gain and improving ACS.[30] These results suggest that olanzapine could serve as a valuable addition to the therapeutic arsenal for CACS, particularly in patients at high risk for chemotherapy-induced nausea and vomiting.[31] Conversely, mirtazapine, another agent with psychiatric indications, showed limited efficacy in promoting weight gain compared to olanzapine, although it demonstrated effectiveness in improving ACS. Notably, mirtazapine was associated with a higher incidence of serious adverse events, which may limit its clinical utility in this context. Taken

together, these findings highlight olanzapine's favorable balance of efficacy and safety, positioning it as a potentially superior option for managing CACS.[32]

Anamorelin and ponsegromab are emerging agents with unique mechanisms of action, offering promising therapeutic options for CACS. Anamorelin, a selective ghrelin receptor agonist, mimics the effects of ghrelin, a hormone known to stimulate appetite and promote anabolic processes.[33] Anamorelin addresses key aspects of CACS by enhancing appetite and increasing lean body mass. However, clinical evidence suggests that while anamorelin improves ACS, its efficacy in promoting significant weight gain remains limited compared to other agents like olanzapine. Ponsegromab, a GDF15 inhibitor, is a monoclonal antibody that targets myostatin, a key regulator of muscle growth inhibition.[34] By inhibiting myostatin, ponsegromab helps preserve muscle mass and potentially reduces muscle wasting in patients with CACS.[35] Clinical studies have demonstrated its efficacy in improving ACS and maintaining weight, positioning ponsegromab as a promising option for CACS management. Despite their novel mechanisms and potential, further research is needed to establish their long-term efficacy and safety profiles and their comparative performance against other agents like olanzapine and anamorelin.

While this meta-analysis provides valuable insights, several questions remain unanswered. Future studies should address the variability in diagnostic criteria for CACS, which limits the generalizability of findings.[36] Establishing standardized diagnostic and outcome assessment criteria is critical for advancing research in this field. Long-term studies are also needed to evaluate the sustained efficacy and safety of these interventions, as most studies included in this analysis had follow-up durations of two to four months. Additionally, head-to-head trials comparing promising agents such as olanzapine and ponsegromab could provide more definitive evidence for clinical decision-making.

285 This meta-analysis has several limitations. First, the included studies exhibited low to
286 moderate heterogeneity in population characteristics, cancer types, and inclusion criteria,
287 potentially affecting the comparability of outcomes. Second, the relatively short follow-up periods
288 in most studies limit the assessment of long-term efficacy and safety. Third, small sample sizes in
289 some studies and potential selection bias contribute to uncertainty in the findings.

290

Conclusion

This meta-analysis highlights the efficacy and safety of pharmacological interventions for CACS, with olanzapine showing notable benefits in promoting weight gain and improving ACS alongside a favorable safety profile. Emerging agents like Anamorelin and Ponsegromab offer promising effectiveness in CACS.

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Data Availability: The corresponding author shall make the datasets available upon reasonable request.

Ethical Statement: Institutional Review Board approval was waived due to the nature of the meta-analysis.

Conflict of Interest: The authors report no conflicts of interest in this work.

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Table 1: Detailed Characteristics of Enrolled Studies

Study	Cases	Age	Male	Therapy	Follow-up	Cancer Types	Inclusion Criteria
Arrieta 2024	71	64	41	Mirtazapine 15 mg daily vs placebo	8w	NSCLC	ACS ≤32 or >5% BW loss last month
Currow 2017	513	62	287	Anamorelin 100 mg daily vs placebo	24w	NSCLC	≥ 5% BW loss within 6m or BMI <20
Dobs 2013	159	66	103	Enobosarm 1 mg or 3 mg daily vs placebo	113d	N.S.	≥ 2% BW loss within 6m
Groarke 2024	187	67	118	Ponsegromab 100 mg, 200 mg, or 400 mg daily vs placebo	12w	Multi	≥ 5% BW loss within 6m or ≥2% BW loss in BMI <20
Hunter 2021	120	54	64	Mirtazapine 15 mg daily vs placebo	8w	N.S.	5% BW loss within 6m or >2% BW loss in BMI <20
Mehrzad 2016	64	52	33	Pentoxifylline 1200 mg daily vs placebo	2m	N.S.	5% BW loss within 2m
Sandhya 2023	124	55	79	Olanzapine 2.5 mg daily vs placebo	14w	N.S.	Cancer-related anorexia within 6m
Stewart Coats 2016	87	57	58	Espindolol 20 mg or 5 mg daily vs placebo	16w	Multi	≥ 5% BW loss within 12m or BMI <20
Takayama 2016	180	65	123	Anamorelin 50 mg or 100 mg daily vs placebo	16w	NSCLC	≥ 5% BW loss within 6m

vs: versus, w: week, d: day, m: month, NSCLC: non-small cell lung cancer, N.S.: not specified, Multi: multi-types of cancers, ACS: anorexia-cachexia scale, BW: body weight, BMI: body mass index

429 Table 2: Summary of Network Meta-Analysis of Pharmacotherapy in Weight Gain

Olanzapin 2.5 mg							
1.34 (-2.6; 5.2)	**Ponsegromab 400 mg**						
2.22 (-1.6; 6.0)	0.88 (-0.18; 1.95)	**Anamorelin 100 mg**					
2.23 (-1.7; 6.1)	0.89 (-0.05; 1.83)	0.01 (-1.03; 1.04)	**Ponsegromab 200 mg**				
2.93 (-0.9; 6.8)	1.59 (0.67; 2.51)	0.71 (-0.31; 1.72)	0.70 (-0.18; 1.58)	**Ponsegromab 100 mg**			
3.28 (-0.6; 7.2)	1.94 (0.65; 3.23)	1.06 (0.12; 1.99)	1.05 (-0.21; 2.31)	0.35 (-0.89; 1.60)	**Anamorelin 50 mg**		
4.43 (0.59; 8.26)	3.09 (1.96; 4.22)	2.20 (1.33; 3.07)	2.20 (1.10; 3.29)	1.50 (0.42; 2.58)	1.14 (0.01; 2.28)	**Mirtazapine 15 mg**	
4.60 (0.82; 8.38)	3.26 (2.35; 4.17)	2.38 (1.82; 2.94)	2.37 (1.50; 3.24)	1.67 (0.82; 2.52)	1.32 (0.41; 2.23)	0.17 (-0.50; 0.84)	**Placebo**

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Table 3: Summary of Network Meta-Analysis of Pharmacotherapy in Anorexia-Cachexia Scale Improvement

Olanzapin 2.5 mg								
6.4 (0.9; 11.8)	**Enobosarm 1 mg**							
6.5 (1.3; 11.7)	0.1 (-4.7; 5.0)	**Ponsegromab 400 mg**						
6.9 (1.6; 12.1)	0.5 (-4.4; 5.4)	0.4 (-3.0; 3.8)	**Ponsegromab 100 mg**					
10.0 (5.8; 14.2)	3.6 (-0.1; 7.3)	3.5 (0.1; 6.9)	3.1 (-0.3; 6.5)	**Mirtazapine 15 mg**				
10.2 (4.2; 16.2)	3.8 (0.4; 7.2)	3.7 (-1.8; 9.2)	3.3 (-2.2; 8.8)	0.2 (-4.3; 4.7)	**Enobosarm 3 mg**			
10.3 (6.1; 14.5)	3.9 (0.2; 7.7)	3.8 (0.3; 7.3)	3.4 (-0.1; 6.9)	0.3 (-1.1; 1.7)	0.1 (-4.5; 4.7)	**Anamorelin 100 mg**		
10.3 (5.1; 15.4)	3.9 (-0.9; 8.7)	3.8 (0.5; 7.1)	3.4 (0.1; 6.7)	0.3 (-3.0; 3.5)	0.1 (-5.4; 5.5)	-0.0 (-3.4; 3.3)	**Ponsegromab 200 mg**	
11.0 (6.9; 15.1)	4.6 (1.0; 8.2)	4.5 (1.2; 7.8)	4.1 (0.8; 7.4)	1.0 (0.1; 1.9)	0.8 (-3.6; 5.2)	0.7 (-0.4; 1.8)	0.7 (-2.4; 3.9)	**Placebo**

435 Table 4: Summary of Network Meta-Analysis of Pharmacotherapy in Serious Adverse Events

Ponsegromab 200 mg						
1.29 (0.08; 20.71)	**Olanzapin 2.5 mg**					
0.78 (0.21; 2.91)	0.61 (0.04; 8.38)	**Anamorelin 100 mg**				
0.69 (0.16; 3.01)	0.54 (0.04; 8.04)	0.88 (0.34; 2.30)	**Anamorelin 50 mg**			
0.59 (0.19; 1.82)	0.46 (0.04; 5.77)	0.75 (0.38; 1.47)	0.85 (0.33; 2.20)	**Placebo**		
0.51 (0.16; 1.59)	0.40 (0.02; 6.49)	0.66 (0.17; 2.50)	0.74 (0.17; 3.32)	0.87 (0.27; 2.79)	**Ponsegromab 100 mg**	
0.18 (0.05; 0.63)	0.14 (0.01; 2.37)	0.23 (0.05; 0.97)	0.26 (0.05; 1.27)	0.30 (0.08; 1.10)	0.35 (0.09; 1.26)	**Ponsegromab 400 mg**

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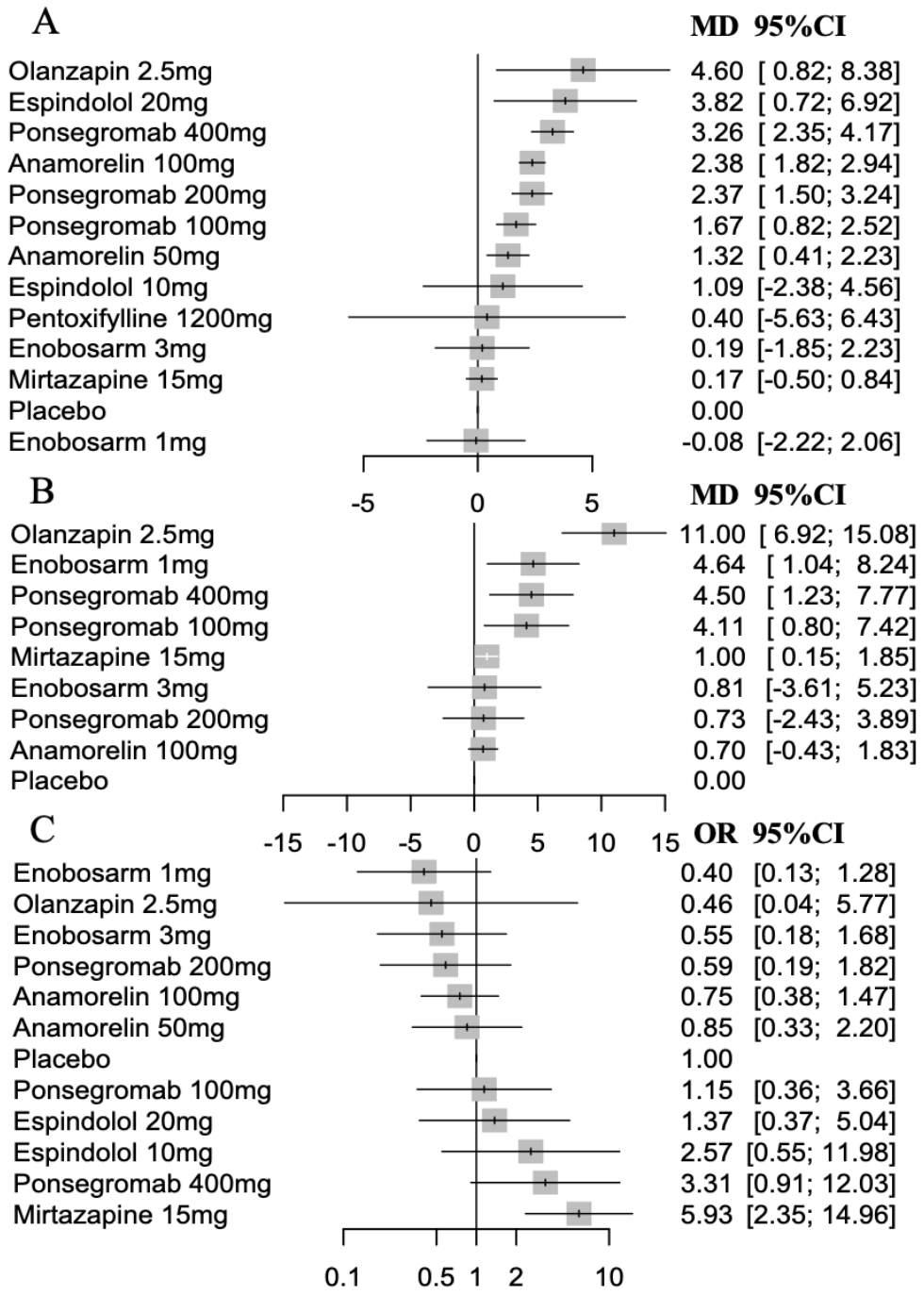
Figure 1: Direct Comparison of Weight Gain Using a Random-Effects Model



A: weight gain, B: anorexia-cachexia scale, C: serious adverse events MD: mean difference, CI: confidence interval, OR: odds ratio