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REVIEW

The effect of oral nutrition supplements and appetite stimulants on weight status among pediatric cancer patients: A systematic review

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Abstract

The objective of this study was to identify the use and impact of oral nutrition supplements (ONSs) and appetite stimulants on weight status among pediatric patients diagnosed with malignancy. We performed a literature search of trials using Medline PubMed, CINAHL, Web of Science Core Collection, Scopus, and Cochrane Database of Systematic Reviews and included all prospective studies except review articles and case-reports/series that assessed ONSs or appetite stimulants among patients (0–20 years old) diagnosed with a pediatric malignancy. Databases were searched through May 17, 2022. There were six trials included with three studies related to ONS and the remaining on appetite stimulants. No studies that compared both ONS and appetite stimulants were found. To assess quality, we used the Risk of Bias in Nonrandomized Studies of Interventions and the Revised Cochrane Risk of Bias Tool for Randomized Trials depending on the study design. The studies all had pediatric patients diagnosed with a variety of malignancy types. All studies demonstrated improvement of weight status in the treatment group across various malignancy types. However, none of the studies addressed nutrition intakes outside of ONS consumption, compliance to ONSs, or frequency of ONS use. Despite the short durations (3–6 months) and significant differences in the timing of intervention initiation (ONS or appetite stimulants), these treatment modalities can improve weight status. Further research is needed to identify the best intervention for improving weight status.

KEYWORDS
appetite stimulant, oral nutrition supplements, pediatrics, weight

OSF registration: https://doi.org/10.17605/OSF.IO/29H8Q

INTRODUCTION

Nearly 60% of patients with a pediatric cancer are affected by cancer-related malnutrition[1] that is multifactorial, encompassing disease burden, treatment side effects, and the intensity of cancer treatment.[2] Those with malnutrition, at any point throughout therapy, have increased infections, higher mortality, and worsened clinical outcomes.[3,4] Malnutrition may progress to cancer cachexia, which is associated with decreased overall survival and is characterized by anorexia, increased inflammation, decreased fat, and decreased muscle mass with subsequent weight loss.[1,3-6]

To support growth and development in the pediatric oncology population, interventions to mitigate weight loss, including oral nutrition supplements (ONSs), appetite stimulants, and enteral nutrition (EN) or parenteral nutrition (PN) (though not a first-line option) are often implemented.[7-9] ONSs, such as complete nutrition supplements or nutritionally dense medical food supplements, are frequently the first intervention used to improve both weight status and calorie and protein intakes.[6,7-9] These interventions have demonstrated increases in weight status in the general pediatric population and in the adult oncology population, but lack data in the pediatric oncology setting.[7-9] Although, ONS have been shown to increase weight status and caloric intakes in the general pediatric population and adult cancer populations, there are concerns with compliance due to palatability, frequency of consumption, and access to ONS.[10] Additionally, there are situations in which oral intakes and ONS in combination are not enough to sustain adequate weight status, thus the use of appetite stimulants may be beneficial to promote higher oral intakes.

Appetite stimulants including megestrol acetate (MA), cyproheptadine (CPH), dronabinol, and mirtazapine have also been used successfully to increase oral intakes and weight status in the general pediatric population.[11] Most of the research in pediatric oncology has studied MA and CPH with a growing body of literature currently on dronabinol.[12-16] Mirtazapine, an antidepressant, is another less commonly used medication in pediatric oncology, with an appetite-stimulating side effect.[14] There have been notable improvements in weight status in the adult oncology populations and general pediatric populations[11-16] when compared with placebos or no stimulant use; however, there are limited data on duration, optimal dosing, and timing of initiation in the pediatric oncology population. Additionally, there are no available data on the use of appetite stimulants in tandem with ONS. When appetite stimulants are ineffective and oral intake is inadequate, a more invasive intervention such as EN and/or PN have been shown to be effective.[17] The gap in evidence makes it difficult to adequately treat the pediatric oncology population with malnutrition or cachexia with less invasive methods such as ONS or appetite stimulants.

Further assessment of the use of appetite stimulants in the pediatric population with a malignancy, including the indication(s) for use, prevalence of use, benefits, optimal dosing and duration, side effects, and success rates, is needed. Without this information, there is a lack of consistency in the initiation of appetite stimulants. Additional information would help direct treatment down more definitive pathways for appropriate timing to trial appetite stimulants compared with using more invasive interventions, such as nutrition support. The specific objective of this systematic review was to determine changes in weight status with the use of ONSs or appetite stimulants among pediatric patients diagnosed with a malignancy.

METHODS

Protocol registration

The protocol for this review was written according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) and registered with Open Science Framework on February 25, 2022; OSF registration: https://doi.org/10.17605/OSF.IO/29H8Q. This systematic review adheres to the PRISMA guidelines.[18,19]

Eligibility

All study types were included in the searches except review articles and case-reports/series. Gray literature, such as abstracts, workshops, and poster presentations were searched, although none met inclusion criteria. No restrictions were imposed on publication year, with the oldest study reviewed being published in 1996. Non-English studies were excluded because of the inability to translate. Patients included children (0 to 20 years old) who had been diagnosed with a pediatric malignancy undergoing active anticancer therapy. The age range included individuals up to 20 years of age because of the potential for pediatric malignancy to progress into the patient's twenties, and the Center for Disease Control and Prevention growth curves included individuals aged up to 20 years old.[20] Primary outcomes include measured weight statuses defined as numerical values (kilograms or pounds and ounces), weight-for-age-and-sex and body mass index (BMI)–for-age-and-sex percentiles, and z

scores, including weight-for-age-and-sex *z* scores (WAZs) and BMI–for-age-and-sex *z* scores (BMIZs). Data on interventions included ONS data (intakes, frequency, and calorie density) and appetite stimulant data (type, dosage, duration, and adverse events).

Information sources and search

Databases searched comprised Medline PubMed, CINAHL, Web of Science Core Collection, Scopus, and Cochrane Database of Systematic Reviews. The search strategy was developed in consultation with the medical librarian (Table 1). The last search was run on May 17, 2022.

Study selection

The EndNote X20 library containing the search results, a total of 250 citations, was imported into Rayyan® to perform the abstract and full-text screening by two independent reviewers.[21] The primary investigator and a coinvestigator screened titles and abstracts of the articles for inclusion without any discrepancies. After review, full-text articles were requested for a total of 26 articles, which were then independently screened in Rayyan by the primary investigator and a coinvestigator. There were no discrepancies, and the articles were screened based on inclusion/exclusion criteria, leaving a total of six citations to be included in the systematic review. Twenty articles were excluded because of the following reasons: articles were written in a foreign language ($n = 2$); articles were a poster presentation, abstract only, or active ongoing trials ($n = 9$); articles used the wrong study design ($n = 4$) where multiple interventions such as nutrition support and ONS were included as one large group with no differentiation; studies used EN/PN as an intervention ($n = 3$); articles did not include a separate pediatric analysis ($n = 1$); and articles that lacked a response from corresponding author ($n = 1$) for full-text request. The full PRISMA diagram can be found in Figure 1.

TABLE 1 Search terms

Theme	Synonyms	Search terms
Pediatric oncology	Neoplasms Cancer Tumor Tumor Oncology Leukemia Neuroblastoma Sarcoma Child Infant Young adult Youth Pediatric	Palliative care Palliative treatment Palliative supportive care Palliative surgery Malignancy Lymphoma Retinoblastoma Pediatrics Adolescent Teen Pediatric
Body weight	Weight gains Weight change Thinness Emaciation Anthropometrics Malnutrition Failure to thrive	Weight loss Weight reduction Underweight Cachexia Wasting Malnourish Nutrition status
Appetite stimulants	Appetite stimulant Anabolic agent Megestrol acetate Mirtazapine Dronabinol Periactin	Cyproheptadine Megestrol Megace Cannabinoid Marinol
ONS	ONS Nutrition therapy Oral supplement Child nutrition	ONS ONS Nutrition supplement

Abbreviation: ONS, oral nutrition supplement.

Data items and extraction

Data were extracted on general information (author, country, funding, and study design), population (sample size, inclusion/exclusion criteria, study patient demographics, malignancy type), interventions (ONS calorie density, frequency of ONS administration, when ONSs were taken in relation to therapy or weight-loss amount that triggered initiation, and adherence to oral nutrition supplementation, indication for appetite stimulant initiation, type, dosage, duration, and adverse events), and outcomes (weight status defined as kilograms, percent change, change in percentiles and *z* scores; timing of intervention initiation and when changes to interventions were made or weight status improvement was noted). *Z* scores are the number of SDs that a child is from the median value (50th percentile) and are noted as the only validated representation of anthropometric data in pediatrics.[22] Negative *z* scores represent percentiles below the 50th, and positive *z* score represent percentiles above the 50th.[22]

Risk-of-bias assessment

The search identified both nonrandomized and randomized controlled trials. Thus, both the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) and the Revised Cochrane Risk of Bias Tool for Randomized

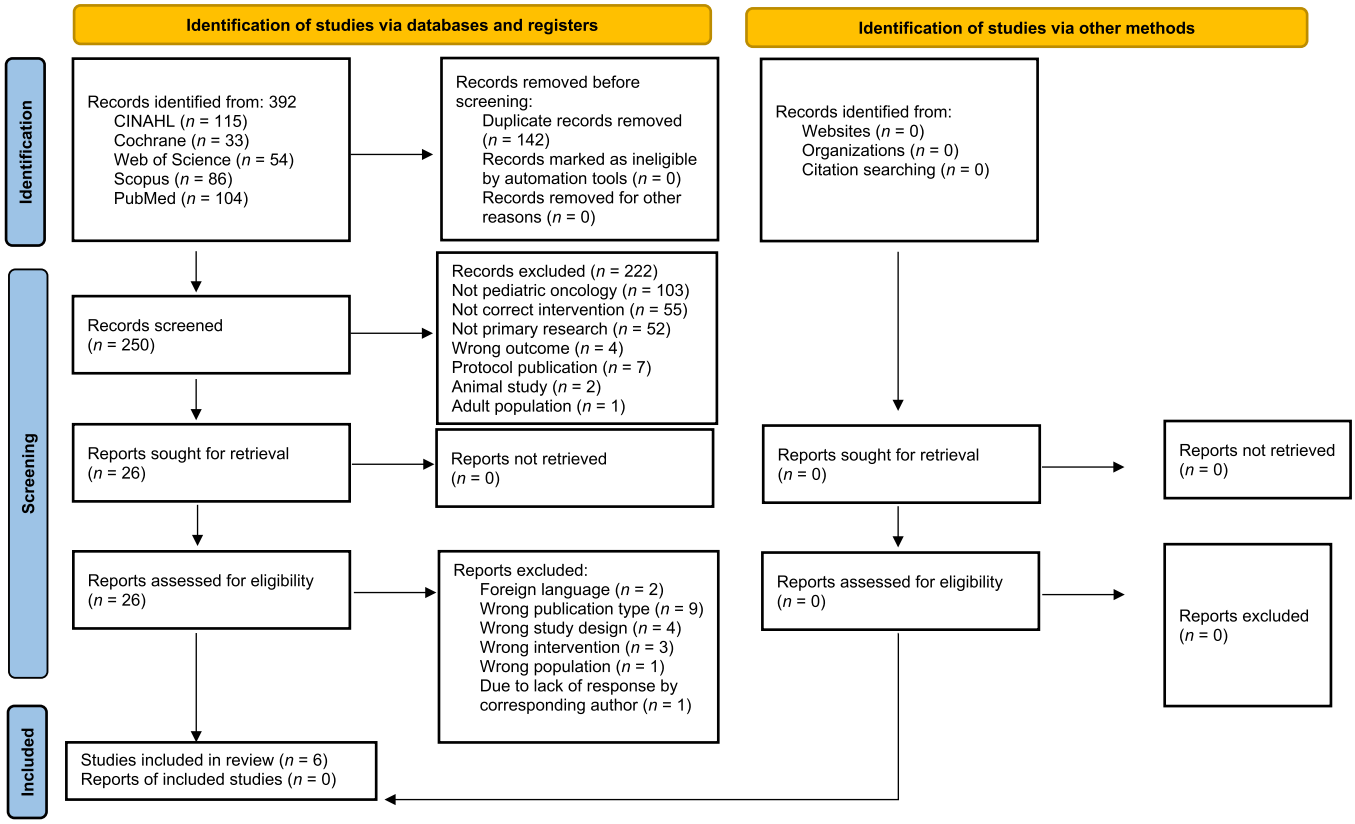

FIGURE 1 Full text screening (PRISMA).

Trials (ROB-2) were used to assess the studies.[23,24] Domains in the ROBINS-I include confounding, patient selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results.[23] Bias in each domain was classified as "low," "moderate," "serious," "critical," or "no information" according to the tools signaling questions.[23] Each study was thus given an overall risk of bias equivalent to the most severe level identified in any of the domains that can be found in Table 2. Domains in the ROB-2 tool include randomization processes, deviations from the intended interventions, missing outcome data, the measurement of outcomes, and the selection of reported results.[24] Bias in each domain was classified as "'low risk," "some concerns," or "high risk."[24] Each study was given an overall risk of bias based on each domain's answer: all "low risk" domains were given a low risk of bias; one "some concerns" domain was given an overall of some concerns; and if there was one or more "high risk" domains or more than one "some concerns" domains, an overall of high risk was given. The risk of bias was assessed independently by the primary investigator and a coinvestigator at the study level. There were no disagreements between risk-of-bias assessments between the two authors; therefore, no third-party arbiter was needed.

RESULTS

Study characteristics

All studies were prospective in design, with one being a randomized controlled trial, another being an open-label phase 2 trial, and the other four studies being either prospective cohort studies or case controlled studies.[6,25-29] All but one study[26] were single site trials conducted internationally (eg, Turkey, Mexico, China, Spain, and Canada); the multicenter study was completed within the United States.[6,25-29] The studies all included children with a pediatric malignancy between 0 and 20 years old with an average age of 6–11 years.[6,25-29] Two studies focused on children diagnosed exclusively with acute lymphoblastic leukemia (ALL), whereas the other studies included a combination of pediatric malignancies.[28,29]

Interventions varied across studies. MA was used in all three appetite stimulant studies, and one study had a combination of CPH and MA.[25-27] In the ONS studies, one used a pseudorandomization to either a 1.0-kcal/ml-formula or one of the two 1.5-kcal/ml-formula options. The allocation was based on meeting 40% of the child's needs.[6] Two studies used liquid supplementation, ranging in caloric density from 1.0 to 1.5 kcal/ml, whereas the third study utilized a 200-kcal supplement bar.[28,29] All

TABLE 2 Risk of bias

Author, year	Confounding	Participation selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall
Risk of Bias in Nonrandomized Studies of Interventions								
Azcona et al, 1996	Serious	Serious	Moderate to severe	Low	Moderate	Low	Low	Serious
Couluris et al, 2008	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Gürlek Gökçebay et al, 2015	Serious	Low	Moderate to severe	Moderate	Moderate	Low	Low	Serious
Gómez-Almaguer et al 1996	Serious	Low	Low	Low	Moderate	Moderate	Moderate	Critical
Liang et al, 2018	Serious	Low	Low to moderate	Low to moderate	Moderate	Moderate to serious	Low	Serious
Revised Cochrane Risk of Bias Tool for Randomized Trials								
Cuvelier et al, 2014	Randomization process, low	Effect of intervention, low	Effect of missing outcome data, low	Effect of measurement of outcome, low	Effect of reported results, low	Overall, low		

studies measured weight status change from baseline to the end of the study period with some including additional time points.[6,25-29] However, the study periods drastically varied from 33 days to 6 months, which could skew results because of the heterogeneity.[6,28,29] No studies compared the use of appetite stimulants to ONSs. All appetite stimulant studies included children who had weight loss as defined by ≥5% or a BMI/age or weight/length less than the tenth percentile.[6,25-29] One study assessed anorexia using a Likert scale to aid in determining appetite initiation.[25] Two of the three ONS studies initiated the intervention at time of diagnosis, whereas the appetite stimulant studies started interventions when weight-loss criteria for the study was met and not necessarily at diagnosis.[6,28] Due to the nature of intervention initiation, the appetite stimulant studies included children presenting with weight loss and the appetite stimulants were used as a treatment of weight loss compared with the oral nutrition supplementation, which started earlier and was described as a preventive intervention.

Study quality

Studies that were analyzed with ROBINS-I revealed four studies at serious risk,[6,25,26,28] and one study at a critical risk.[29] The one study that was analyzed with the ROB-2 was determined to be at low risk, as demonstrated in Table 2.[27] Weaknesses included participation selection (patients were chosen specifically after they had a specified amount of weight loss), missing data (adherence and frequency of oral nutrition supplementation were unreported and unclear if all patients finished the study), deviations from interventions (it was unclear on how supplements 1.0 kcal/ml vs 1.5 kcal/ml were allocated), and measurement of outcomes (lack of information regarding current oral intakes outside of supplements, and supplement adherence).

ONSs

Demographic data

Two of the studies included 0- to 14-year-old patients, whereas one study provided no age range of included patients (Table 3).[6,28,29] The age of patients in these studies were all similar, with a mean age of 8.7 ± 4.9 years old for the study by Gürlek Gökçebay et al, a median age of 6 years (2–11 years old) for the study by Gómez-Almaguer et al, and a range of 1–14 years old for the study by Liang et al.[6,28,29] Inclusion criteria varied

TABLE 3 Data extraction of included ONS studies

First author and year	Study location	Design	*N*, age ± SD	Malignancy type	Oral nutrition supplement	ONS dose, duration	Weight status measure	Mean weight status measure
Gürlek Gökçebay 2015	Turkey	Prospective cohort	45, 8.7 ± 4.9 (mean)	31% HL, 16% NHL, 18% NB, 8% EWS, 8% RMS, 6% CNS, 2% Osteosarcoma, 2% HNC, 2% Wilms, 2% Hepatoblastoma, 2% LCH	Pediasure 1 kcal/ml ($n = 8$, 31%) or Pediasure plus 1.5 kcal/ml vs Resource 1.5 kcal/ml ($n = 18$, 69%). Did not analyze the 19 patients who did not receive ONS	NR, 6 months	Weight (kg), BMI percentile, WFA percentile, WAZ, BMIZ	WAZ: −0.85 at diagnosis, −0.7 at 3 months, −0.84 at 6 months ($P < 0.001$). BMIZ: −0.93 at diagnosis, −0.78 at 3 months, −0.44 at 6 months ($P = 0.003$).
Gómez-Almaguer 1996	Mexico	Prospective cohort	31, 6 years (median)	Standard-risk ALL	Vita-snack bar, 200 kcal ($n = 31$)	1 bar per day, 3 months	Weight (kg)	Well-nourished: 19.3 vs 20.3 kg ($P < 0.01$) from baseline to 3 months. Malnourished: 18.9 vs 19.8 kg ($P < 0.01$) from baseline to 3 months
Liang 2018	China	Prospective-matched cohort	127; 35 ONS (1–5 years), 25 ONS (6–13 years); 38 control (1–5 years) 29 control (6–13 years); Age described as a range	ALL	Peptamen, 1.0 kcal/ml ($n = 60$, 47%)	Three to five times per day, 33 days	Weight (kg)	ONS group 0.07 ± 0.95 kg of weight gain vs control group 0.77 ± 2.66 kg ($P = 0.001$) from baseline to day 33

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; BMIZ, BMI for age *z* score; CNS, central nervous system; EWS, Ewing's sarcoma; HNC, head and neck cancer; HL, Hodgkin's lymphoma; LCH, Langerhans' histiocytosis; NB, neuroblastoma; NHL, non-Hodgkin's lymphoma; NR, not reported; ONS, oral nutrition supplement; RMS, rhabdomyosarcoma; WFA, weight for age; WAZ, WAF *z* score.

among studies because Gürlek Gökçebay et al and Liang et al enrolled patients that were newly diagnosed, but Gómez-Almaguer et al enrolled patients who were in complete remission and receiving active treatment for at least 3 months (range, 3–18 months).[6,28,29] Liang et al had an additional criteria of a positive malnutrition screening score of >4 using the Screening Tool for Assessment of Malnutrition in Pediatrics (STAMP) tool.[28]

Liang et al and Gómez-Almaguer et al included only children diagnosed with ALL.[28,29] Gómez-Almaguer et al's study was specific to children with standard-risk ALL only, whereas Liang et al did not describe the ALL stratification among patients.[28,29] Gürlek Gökçebay et al had varied malignancies within the study as described in Table 3.[6] Importantly, 51% of these patients were considered to have advanced cancer (stage 3–4).[6] All studies excluded patients who were unable to consume oral foods or were receiving EN or PN.[6,28,29]

Gürlek Gökçebay et al enrolled 50 patients, of which 45 completed the study, 3 died, and 2 abandoned therapy.[6] Of the 45 who completed the study, 26 received ONSs due to a malnutrition diagnosis and 19 received no ONS.[6] Malnutrition was diagnosed by meeting one criteria of either BMI less than the fifth percentile, ideal body weight less than the 90th percentile, triceps skinfold test or midupper arm circumference less than the fifth percentile, or >5% weight loss at diagnosis.[6] Those who were diagnosed with malnutrition were then randomized to either hypercaloric vs isocaloric supplementation, defined as 1.5 kcal/ml and 1.0 kcal/ml, respectively.[6] Gómez-Almaguer et al enrolled 31 patients and analyzed preintervention and postintervention data for all enrolled patients.[29] Liang et al enrolled 127 patients, of which 60 received ONSs and 67 were the control group.[28] All patients in this study were placed on a low-fat diet; however, due to concerns for hepatic toxicity and pancreatitis with the use of a specific chemotherapy, L-asparaginase was used in induction therapy.[27] Liang et al were able to analyze all 127 enrolled in the study.

Gürlek Gökçebay et al reported baseline WAZ, with four patients (9%) having a WAZ < -2, whereas 46 (91%) had WAZ > -2 and 20 (44%) had a BMI < 5%tile (representing malnutrition).[6] Additionally, height-for-age z score (HAZ) < -2 was found in 4 (9%) participants at baseline and 5 (11%) participants by the end of the study.[6] Gómez-Almaguer et al had no significant differences between the well-nourished and malnourished groups' baseline weight, 19.3 vs 18.9 kg, respectively.[29] Malnutrition was defined as more than at least one SD from the tenth percentile for weight for age and definite signs of malnutrition, including failure to thrive, hair loss, edema, and skin changes.[29] There was also no significant difference between height pretreatment and posttreatment for either group (1.09 vs 1.11 m and 1.06 vs 1.09 m), respectively,[29] although there was no adjustment made for age or sex, limiting the ability to assess how these children compare with their age- and sex-matched peers. Similarly to Gómez-Almaguer et al, Liang et al only analyzed weight and did not adjust for sex and age. Liang et al found no significant differences between baseline weight of the ONS and control groups, 18.9 ± 7.72 kg vs 21.0 ± 10.5 kg, although there were no height data collected.[28] Without data for height, it is difficult to discern the overall weight status of the patient and if there is stunting present. Additionally, there is no ability to assess the BMI or weight-for-length for categorization of malnourished vs overweight or obese.

ONS used/dosage/duration

All three studies used different ONS methodologies, including a powder mixed into 150 ml of water, ready-to-feed supplements, and a supplement bar (Table 3).[6,28,29] Gürlek Gökçebay et al provided patients with supplements that met 40% of their recommended dietary allowance (RDA)[6] using either Pediasure® (1 kcal/ml), Pediasure® plus (1.5 kcal/ml), or Resource® (1.5 kcal/ml).[6] Liang et al mixed 39 g of Peptamen® powder with 150 ml of water (1 kcal/ml) and provided it 3–5 times per day for 33 days starting at diagnosis and lasting through the first month of therapy.[28] Gómez-Almaguer et al provided a 200-kcal nutrition bar once per day, meeting 35% of the RDA, for 3 months starting at diagnosis.[29] Although all three studies started supplementation at diagnosis, Gómez-Almaguer et al was the only study to describe the frequency of and adherence to supplement consumption.[29] Although it was reported that 93.5% had "good compliance," it is unclear how compliance was measured.[6,28] All three studies had varying durations of the intervention (1, 3, and 6 months) and only one provided a description of oral intakes of study patients used to analyze total intakes and percentage of RDAs being met.[6,28,29]

Weight status changes with ONS use

All studies saw a significant increase in weight status with the ONS intervention compared with baseline or control groups.[6,28,29] Gómez-Almaguer et al compared pretreatment and posttreatment weight statuses of oral nutrition supplementation and noted that in both groups (well-nourished and malnourished), weight status increased with the use of ONSs.[29] The well-nourished group increased from 19.3 to 20.3 kg ($P < 0.01$) and the

malnourished group increased from 18.9 to 19.8 kg ($P < 0.01$).[29] Height was also measured preintervention and postintervention with significant differences between all groups ($P < 0.01$).[29] However, it is difficult to interpret these changes because neither height nor weight were adjusted for age and sex to compare participants with their age- and sex-matched peers. Liang et al saw similar results with ONSs during the induction phase, or first month of ALL therapy.[28] The group consuming ONSs demonstrated a 0.07 ± 0.95 kg weight gain vs weight loss in the control group of 0.77 ± 2.66 kg ($P = 0.001$).[28] Moreover, Liang et al prescribed both the ONS and control group a low-fat diet, and despite a low-fat diet, the ONS group was able to gain weight.[28]

Gürlek Gökçebay et al had 26 patients that received ONSs and 22 of those met criteria for malnutrition.[6] Of those 26 patients who received ONSs, 18 received hypercaloric supplementation (1.5 kcal/ml) and 8 received isocaloric supplementation (1.0 kcal/ml).[6] With supplementation, rates of malnutrition had decreased from baseline ($n = 22$, 49%) to 3 months ($n = 14$, 31%) and 6 months ($n = 11$, 24%) ($P < 0.006$).[6] Additionally, the ONSs group saw a decrease in the number of patients with an ideal body weight of less than 90th percentile ($P = 0.015$) and BMI less than the fifth percentile ($P = 0.003$) from baseline to 6 months.[6] Furthermore, there was a significant increase in the number of patients with a weight-for-age less than the 90th percentile from baseline to 3–6 months ($P < 0.001$).[6] Improvements were also found in z scores and percentiles throughout the study between baseline and 6 months: WAZ (−0.85 vs −0.84, $P < 0.001$), HAZ (−0.51 vs −0.77, $P < 0.001$), and BMIZ (−0.93 vs −0.44, $P = 0.003$), weight-for-age percentile (89.1% vs 90.2%, $P < 0.001$), and weight-for-length percentile (94.6% vs 99.5%, $P = 0.003$).[6] Interestingly, there was no further analysis or comparison to the patients who did not receive any supplementation.

Summary of ONS

These three studies concluded that ONS is helpful in improving weight status for patients with a pediatric malignancy.[6,28,29] Despite the improvements in weight statuses noted, there are still many limitations to these studies, including short duration, lack of nutrition intake analysis, and lack of consideration of the severity of treatment or types of chemotherapy received. These studies varied in duration from 1[28] to 6 months.[6] The short duration of these studies does not align with the initiation or duration of the participants chemotherapy regimen. Furthermore, the inconsistency in duration makes it challenging to draw conclusions on the most effective duration for ONS use. There are additional limitations surrounding when patients were enrolled in the studies. Two studies enrolled children at diagnosis and one study enrolled children when they were in remission for 3 months. In the Liang et al study, patients were included during their first month of ALL therapy.[28] The difficulty with this duration is the validity of the weight gain since the first month of ALL therapy includes a month-long use of daily steroids. Steroids can have a side effect of causing weight gain and fluid retention, making it challenging to know whether the weight gain was due to the use of ONSs or skewed by the steroid use, especially considering both the intervention and control group saw significant increases. Additionally, Gürlek Gökçebay et al did not compare children who were taking a supplement to a control group. Gürlek Gökçebay et al also limited the analysis to how weight changed in children with the use of ONSs but did not compare weight changes to those without ONS.

Different malignancy types can also skew outcomes as treatment therapies can vary drastically. One study[6] had varying malignancy types, whereas two studies were solely ALL patients. The studies among ALL patients still varied, however. One of the studies was among standard-risk ALL patients,[29] whereas the other study did not mention the risk stratification of ALL patients.[28] This is an important factor as high-risk ALL patients receive more intense chemotherapy regimens that may alter ability to improve weight status. The lack of nutrition intake analysis outside of ONS consumption and estimation of the percentage of energy needs met by ONS interventions are additional limitations to these studies. Two studies reported the choice of supplements based on 35%–40% of the RDA; however, there was no mention of adherence to the supplements and if the amount consumed was able to meet the intended percentage of the RDA.[6,29] Furthermore, in the Gürlek Gökçebay et al study, they mentioned a dietitian who chose between isocaloric or two hypercaloric ONSs for the patients based on 40% of RDA but never described which hypercaloric ONS was given or provided any data on which supplement was utilized and when.[6] Lastly, there was no standardization of ONS across the studies. Each study utilized a different supplementation type, quantity, calorie density, and frequency. If each study met a specific percentage of RDAs with the use of similar formulations, studies would be more comparable.

APPETITE STIMULANTS

Demographic data

These studies included 0- to 20-year-old patients diagnosed with a pediatric malignancy, which varied between solid tumors and hematological malignancies (Table 4).[25-27]

TABLE 4 Data extraction of included appetite stimulant studies

First author, year	Study location	Design	*N*, age, (years)	Malignancy type	Appetite stimulant	Stimulant dose, duration	Weight status measure	Mean weight status measure
Azcona, 1996	Spain	Prospective case control	35 prospective patients and 59 historical charts, 11.4 years (mean)	11 osteosarcomas, 11 EWS, 4 lymphomas, 5 brain tumors, 2 NB, 1 neurofibrosarcoma, and 1 RMS	MA	10 mg/kg/day (maximum dose, 240 mg/day), 3 ± 1.5 months (mean)	Weight (kg) and BMI	Weight in MA group was greater at 3 months ($P < 0.05$), 6 months ($P < 0.01$), and 12 months ($P < 0.001$). BMI was significantly higher in the treatment group ($P < 0.001$).
Couluris, 2008	USA multicenter	Open-label phase 2 trial	66, 11.7 years (median)	19 leukemia, 15 sarcoma, 13 brain tumor, 6 lymphoma, 1 hepatic tumor, 1 Wilms' tumor, 1 NB, and 13 other types	CPH and MA	CPH: 0.25 mg/kg/day orally, divided into two doses (maximum dose, 20 mg/kg/day), up to 12 weeks. MA: 10 mg/kg/day in a single daily dose, 4 weeks	WAZ and weight (kg)	CPH: mean weight gain was 2.6 kg (38.91 vs 41.5 kg, $P = 0.001$). WAZ average change was 0.35 (-0.66 vs -0.31, $P = 0.001$). Weight gain between hematologic and solid tumor diagnoses (2.90 vs 2.39 kg, $P = 0.46$). WAZ differences between hematologic and solid tumor diagnoses (0.31 vs 0.38, $P = 0.95$).
Cuvelier, 2014	Canada	Randomized, double-anonymized, placebo-controlled clinical trial	26, 9.7 years on MA arm and 12.5 years on placebo arm (mean)	MA arm: 1 osteosarcoma, 1 EWS, 5 medulloblastoma, 1 NB, 2 AML, 1 relapsed ALL, 1 HL, 1 RMS. Placebo arm: 2 osteosarcoma, 1 EWS, 2 medulloblastoma, 2 NB, 2 AML, 1 lymphoblastic lymphoma, 1 GCT	MA	7.5 mg/kg/day (maximum dose of 800 mg/day), 90 days	WAZ, BMIZ, and weight (kg)	Percent weight change: $+19.7\% \pm 15.3\%$ (MA) vs $-1.2\% \pm 4.9\%$ placebo ($P = 0.003$). WAZ: $+1.00 \pm 0.79$ vs -0.18 ± 0.34 ($P = 0.002$). BMIZ: 1.58 ± 1.37 vs -0.29 ± 0.50 ($P = 0.006$).

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; BMIZ, BMI *z* score; CPH, cyproheptadine; EWS, Ewing's sarcoma; GCT, germ cell tumor; HL, Hodgkin's lymphoma; MA, megestrol acetate; NB, neuroblastoma; RMS, rhabdomyosarcoma; WAZ, weight-for-age *z* score.

Azcona et al and Cuvelier et al enrolled patients when they had met the requirement of at least 5% weight loss at any point throughout therapy, whereas Couluris et al enrolled patients when they met a diagnosis of cancer cachexia defined as weight loss of ≥5%, decrease in two percentile ranks, or weight/height less than the tenth percentile.[25-27] Azcona et al and Cuvelier et al also considered a stimulant if the patient was diagnosed with anorexia; however, Azcona et al's study was the only study that defined anorexia with the use of a 5-point Likert scale.[25] Scores were defined as very poor appetite, poor, fair, good, and very good, 1–5 respectively, with a score of ≤3 qualifying as having anorexia.

The mean ages of these studies were all similar at 11.4 years old for Azcona et al, 11.7 years old for Couluris et al, and 9.7 years old for Cuvelier et al.[25-27] Malignancy types varied and included osteosarcoma, Ewing's sarcoma, lymphomas, central nervous system tumors, neuroblastoma, rhabdomyosarcoma, neurofibrosarcoma, hepatic tumors, Wilms' tumor, germ cell tumor, and leukemias. Azcona et al's article was the only study that restricted itself to solid tumors only,[25] and Cuvelier et al's article was the only study in which all cases were considered high-risk diagnoses or were undergoing intensive therapy.[27] All studies excluded individuals undergoing concomitant treatment with corticosteroids for at least 7 days throughout the study as this could impact appetite. Additionally, Cuvelier et al also excluded those who received steroids within 14 days of enrolling into the trial.[27] Couluris et al and Cuvelier et al excluded any patients receiving PN or EN,[26,27] and although Azcona et al did not specifically exclude those patients, no patient in their study was reported to be receiving EN or PN.[25] Azcona et al compared 35 intervention patients to 59 historical charts who received the standard of care, whereas Cuvelier et al assigned 26 patients 1:1 to either MA or placebo drug and standard of care.[25,27] Couluris et al felt that randomization was not safe for their patient population, thus enrolled 70 patients to CPH; if they were deemed nonresponsive to treatment, defined by no weight gain or further weight loss, they then met criteria for a trail of MA if accepted by patient and provider.[26]

Weight statuses were assessed in both Couluris et al's and Cuvelier et al's studies.[26,27] Couluris et al had a mean baseline weight of 38.91 ± 16.10 kg, whereas Cuvelier et al had a mean baseline weight of 33.6 kg in the MA arm and 40.1 kg in the placebo arm.[27] Couluris et al's study has a mean baseline WAZ of -0.66 ± 1.22,[26] whereas Cuvelier et al's study had a WAZ and BMIZ that were −0.87 and −0.97 for the MA arm and −0.24 and −0.52 for the placebo arm, respectively.[27] Neither noted a significant difference between groups. Azcona et al had no significant differences in weight status at baseline between groups, but a specific z score value was not provided.[25] Interestingly, Cuvelier et al's article was the only study to report percentage weight loss at study entry, which was on average 9.1% for the MA group and 10.2% for the placebo group.[27] Additionally, Cuvelier et al's article was the only study to analyze HAZ to help better define changes in BMIZ at baseline but, unfortunately, did not continue to analyze throughout the study.[27] There was no significant difference in HAZ between groups, -0.19 ± 0.12 vs -0.03 ± 0.14 ($P = 0.1$).[27]

Appetite stimulant type/dosage/duration

Two of the studies used MA as the only appetite stimulant, but one study used CPH as the initial appetite stimulant and then switched to MA for nonresponsive patients.[25-27] Azcona et al started MA at 10 mg/kg/day, and Couluris et al started at the same dosage for nonresponsive patients; however, Cuvelier et al started at 7.5 mg/kg/day.[25-27] MA was used for a mean of 3 months (range of 1–6 months) in the Azcona et al study, whereas the Cuvelier et al study used MA for a mean of 90 days with 70% completing the full 90-day period.[25,27] Couluris started with CPH 0.25 mg/kg/day divided into two doses for up to 12 weeks.[26] Participants were assessed for response to CPH at 4, 8, and 12 weeks. If participants had no response at 4 weeks, defined as no weight gain or additional weight loss, they were transitioned to MA for a 4-week trial at 10 mg/kg/day once a day. Azcona et al's article was the only study that reported a mean dose throughout the study, which was 240 mg/day,[25] whereas Couluris et al and Cuvelier et al reported a maximum dose of 20 mg/kg/day of CPH and 800 mg/day of MA, respectively.[26,27]

Weight status changes with appetite stimulant use

All studies saw a significant increase in weight status, either from baseline to end point, or when compared with control groups, with the use of an appetite stimulant (Table 4).[25-27] Azcona et al noted a mean weight gain of $13.1\% \pm 2.63\%$ for those receiving MA.[25] Weight was significantly higher in the MA group at month 1 ($P < 0.001$), 3 ($P < 0.05$), 6 ($P < 0.01$), and 12 ($P < 0.001$) compared with the control group, which had persistent weight loss during the first 6 months.[25] Additionally, BMI was significantly higher in the MA group at month 3 ($P < 0.001$), 6 ($P < 0.001$), and 12 ($P < 0.01$) compared with control.[25] Appetite scores, measured using a Likert scale, were also significantly increased in the first month ($P < 0.001$) compared with baseline but there was no

further assessment throughout the rest of the study duration.[25] Moreover, there was a statistically significant moderately positive correlation between use of MA and appetite score ($r = 0.4$, $P < 0.01$) at 1 month.[25]

Cuvelier et al saw no significant difference between MA and placebo group.[27] Although there were no differences in weight status at baseline between the groups, after MA therapy (90 days), there were significant differences between the MA and placebo groups in mean percent weight change ($+19.7\% \pm 15.3\%$ vs $-1.2\% \pm 4.9\%$, $P = 0.003$), WAZ ($+1.00 \pm 0.79$ vs -0.18 ± 0.34, $P = 0.002$), and BMIZ (1.58 ± 1.37 vs -0.29 ± 0.50, $P = 0.006$), respectively.[27] The percent weight change at the end of the study compared with highest pre-enrollment weight was also significantly different between the two groups ($+9.3\% \pm 15.7\%$ vs $-11.0\% \pm 9.4\%$, $P = 0.018$).[27] Interestingly, 3 out of 10 placebo patients were withdrawn from the study to initiate EN/PN due to excessive weight loss (>15%), whereas no patients (0 out of 13) on the MA withdrew or were forced to withdraw from the study.[27]

Couluris et al had 50 out of 66 CPH patients respond to therapy at 4 weeks.[26] Forty-eight had a mean weight gain of 2.6 kg from baseline to end point (38.91 vs 41.5 kg, $P = 0.001$), and two had weight stability.[26] Mean WAZ also increased from baseline by 0.35 (-0.66 vs -0.31, $P = 0.001$). Of the 16 nonresponsive patients, they had a mean weight loss of -1.46 kg and mean WAZ decrease of -0.28.[26] Couluris et al further categorized all patients by age, <9 years old, 9–13 years old, and >13 years old, to assess the difference in weight and WAZ changes. Among all participants there was a significant difference in weight gain based on age ($P = 0.05$), with those in the oldest group having the greatest increase in weight. When assessing weight change by response to CPH, the highest weight gain was noted among the oldest group (+0.85 kg vs +1.7 kg vs +3.6 kg, respectively, $P = 0.003$). Although there were significant differences across the age group, weight increases noted only in kilograms, as compared with percent weight gain, does not provide adequate detail.[26] However, when looking at an age-adjusted measurement and WAZ change among the total sample, there was no statistically significant difference among the age groups. When assessing WAZ change among a age group based on response to CPH, there was no significant differences found within the response groups, although the CPH responders had increases in WAZ, whereas the nonresponsive patients had decreases in WAZ. Interestingly, there was a significant difference between the response rate to CPH based on hematologic and solid tumor malignancy types (91.3% vs 67.4%, $P = 0.04$),[26] although weight change and WAZ remained insignificant between hematologic and solid tumor malignancy types (2.9 kg vs 3.9 kg, $P = 0.45$ and 0.31 vs 0.38, $P = 0.95$), respectively.[26]

Appetite stimulant summary

All three studies found that the use of an appetite stimulant, MA or CPH, is an effective intervention to improve weight status for children with pediatric cancer–related or cancer/treatment–related weight loss, anorexia, or cachexia.[25-27] Though the evidence demonstrates these two appetite stimulants can improve weight status, there are multiple limitations among these studies. First and foremost, only two appetite stimulants were studied, and only one study compared the intervention to a placebo.[25-27] Additionally, no study directly compared appetite stimulants to identify which may be more effective in this population. The duration of these studies was relatively short (3–6 months) considering the duration of cancer treatments can vary from 6 months to ≥3 years. Consistency of intervention initiation based on weight loss was present (≥5% weight loss), although Cuvelier et al had a baseline of 9% and 10% weight loss prior to intervention for MA and placebo group, respectively.[27] Anorexia as an additional criterion for starting an appetite stimulant was used, although anorexia was only operationally defined by Azcona et al. The timing of the intervention in relation to diagnosis or current place in treatment was not well described.

Only one study performed a subanalysis by different malignancy groups to assess the response to the appetite stimulant.[26] Different malignancy types have different survival outcomes, treatment intensities, and regimens, which can skew the response to interventions and alter weight status response. More analysis of hematologic vs solid tumor malignancies should be a focus in future studies to provide better guidance for clinical practice. Furthermore, there was no nutrition intake assessment or analysis, or nutrition-focused physical exam (NFPE) to better assess nutrition status done for any of these studies. One of the side effects of MA is edema and water retention.[27] Without analysis of nutrition intake or assessment of edema through NFPE, it is difficult to know if weight changes were because of fluid retention, an increase in nutrition intakes, or confounding variables such as the concomitant use of ONSs. Lastly, Couluris et al did not analyze or assess any data for the nonresponsive patients once they made the change to MA from CPH.[26]

DISCUSSION

This review analyzes ONSs and appetite stimulants as interventions for pediatric patients with a malignancy who may or may not already be experiencing weight loss. Often, pediatric patients with a malignancy struggle to maintain weight status because of the complications from therapy. It has been well described that nutrition and weight status

make important impacts on overall survival, treatment tolerance, infection rates, and number of hospitalizations or length of stays,[1,3,4] yet data on the best or most effective intervention to maintain weight status have not been well described. In pediatrics, the only validated measure of nutrition status are *z* scores for age.[30] Many studies, however, utilize various weight measurement modalities as a marker of nutrition status, which is why this review chose weight status as its primary outcome.

The studies included in this systematic review have demonstrated that both ONSs and appetite stimulants can positively affect weight status among patients with a pediatric malignancy.[6,25-29] The use of MA and CPH both were proven to be a successful intervention to increase weight status, while taking into consideration the potential confounding steroid use as a cancer therapy by excluding those patients.[25-27] It does appear that about 3 months of use was effective in improving weight status, though the impact of continued use after 3 months requires further research. Similarly, the use of ONSs was effective in improving weight status, although key factors, such as treatment medications and dietary intake, were not controlled for or were not reported. Without data on these key factors, it is unclear if the weight gain is related to ONS intake alone.[6,28,29] Comparable to appetite stimulants, a duration of 3 months of use was identified as effective in improving weight status, yet the impact of continued use past that time requires additional research.

Additional limitations include a lack of randomized control trials, and the risk of bias was high in five of the six studies, with four studies at serious risk of bias and one at critical risk of bias. Subsequently there was also a lack of subgroup analysis within malignancy type groups, further limiting the ability to draw conclusions on the effectiveness of interventions in specific malignancy groups. Subcategorizing malignancy types can help manage confounding variables due to variances in therapy.

Implications for practice and research

This review provides evidence that appetite stimulants or ONSs can be a useful intervention for patients with a pediatric malignancy who are struggling with maintaining their baseline or normal weight status. There were no data on whether an ONS vs an appetite stimulant is a better intervention for improving weight status. Additionally, there are no data on whether different malignancy types would respond to a specific intervention better. However, the Couluris study demonstrated greater weight status improvement in those treated with CPH who had hematologic malignancies compared with those with solid tumor malignancies.[26] This may be suggestive of needing to use a different appetite stimulant depending on the type of malignancy, although more research is needed. There is currently not enough data to support a clinical practice guideline for the use of ONSs vs appetite stimulants to improve weight status among pediatric patients with a malignancy. The lack of studies comparing the two interventions limits the ability to draw conclusions on which intervention may be more effective for improving weight status. More research is needed to be able to develop clinical practice guidelines to help manage this population more effectively. Furthermore, the use of consistent criteria to identify malnutrition, such as *z* scores for age or the American Society for Parenteral and Enteral Nutrition/Academy of Nutrition and Dietetics malnutrition criteria, could allow for more direct comparisons among studies.

This systematic review provides some data to support the use of appetite stimulants or ONS for patients with a pediatric malignancy struggling with weight status. Future studies need to focus on consistency among the interventions (ie, caloric density, dosage, and duration). Additional subgroup analysis into malignancy types (hematological vs solid tumors), would be extremely beneficial as well. The treatment drugs and intensities vary drastically between hematological and solid tumor diagnoses, which can significantly alter weight and nutrition status of patients. Subcategorizing them would allow for analysis of each group to determine if one method is superior to another. The subcategorization may lead to small sample sizes affecting the power of the studies, which could be addressed by decreasing population variance and increasing the effect of interest. Assessment and analysis of the nutrition intakes and incorporation of NFPE of patients are needed to better understand the effects of these interventions. In the studies including ONSs as the intervention, compliance, frequency of consumption, percent of RDA met, and ONS palatability should also be outcomes assessed as these would help identify if there are difficulties with compliance. Supplements with different caloric densities can also be compared, although analysis to assess if there is a difference in acceptance, tolerance, and weight status changes by calorie density should be assessed.

CONCLUSION

In conclusion, this systematic review has shown that the use of appetite stimulants or ONSs can improve weight status among patients with a pediatric malignancy. Based on the available studies, the selection between the use of appetite stimulants or ONSs is not able to be determined. Despite the limitations in the available literature, this is the first systematic review to evaluate the effect of appetite stimulants or ONSs on weight status among pediatric

patients with a malignancy. Future studies need to better describe nutrition intakes and have consistency among interventions used, criteria for malnutrition, and use age- and sex-adjusted weight status measurements, as these will improve the available evidence and help guide clinicians. Malnutrition and a poor weight status have been shown to negatively affect treatment outcomes for pediatric malignancies, yet the use of appetite stimulants or ONSs can be an effective method for improving weight statuses.

AUTHOR CONTRIBUTIONS

Corey Hawes and Laura Byham-Gray contributed to the conception and design of the research. Stephanie Henderson, Corey Hawes, and Alison Gomes contributed to the acquisition and analysis of the data. Corey Hawes and Alison Gomes contributed to the interpretation of the data. Corey Hawes drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

CONFLICT OF INTEREST

None declared.

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