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Review Article

Appetite stimulant before meal aids faster recovery from illness: a comprehensive review

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ABSTRACT

Loss of appetite (LOA), or anorexia, is a significant health concern that can arise due to various factors such as age, illness, or medication, leading to nutritional deficiencies and impacting overall health and quality of life. LOA can be categorized as acute or chronic, with the latter often associated with serious underlying conditions, including cancer and chronic diseases. This review explores the multifactorial causes, prevalence, and health consequences of LOA, emphasizing the importance of early diagnosis and intervention. A multi-centre survey conducted in India revealed a striking prevalence of LOA, affecting 93.1% of 15,914 participants, particularly those with infectious diseases. Effective management strategies are critical, with tools like the Council on Nutrition Appetite Questionnaire (CNAQ) aiding in the assessment of appetite. Pharmacological interventions, including appetite stimulants, play a role in enhancing food intake, while the combination of multivitamins, zinc, and lysine has been found to support appetite stimulation and improve nutritional status. Understanding the complex interplay of physiological, psychological, and pharmacological factors is vital in developing standardized guidelines for managing LOA. Increasing awareness regarding early diagnosis and timely management is essential to improve nutritional status and quality of life for affected patients.

Keywords: Anorexia, Appetite stimulants, Lysine, Loss of appetite, Multivitamins, Nutritional deficiencies

INTRODUCTION

Hunger is a physiological response to a lack of food, driven by biological mechanisms like low blood glucose levels, hormonal changes, and signals from the hypothalamus. It represents the body's objective need for sustenance to maintain energy balance. In contrast, appetite is the psychological desire to eat, influenced by external factors such as sensory cues (sight, smell, and taste of food), emotional states, and social or cultural contexts. It is possible for appetite to occur without hunger, such as when craving dessert after a full meal, or for hunger to exist without appetite. Understanding these distinctions is essential for examining eating behaviours and their implications for health.[1] Loss of appetite (LOA), or anorexia, refers to a reduced or absent desire to eat, which can occur due to various factors such as age, illness, or medication. This condition has significant health implications, leading to nutritional deficiencies that can negatively affect a patient's overall health, well-being, and quality of life. LOA may present either as a short-term issue, often related to temporary illnesses or digestive problems, or as a long-lasting condition caused by more serious underlying health issues.[2,3]

Acute LOA typically manifests as a temporary reduction in appetite, often triggered by infections or inflammatory responses. Symptoms include fatigue, fever, and a preference for carbohydrates over protein to meet the body’s energy demands during the acute phase. While chronic LOA is associated with persistent loss of appetite, resulting in significant weight loss, muscle wasting, and malnutrition. Symptoms include anaemia, extreme weakness, and increased vulnerability to infections. It

commonly occurs in diseases like cancer, HIV, and rheumatoid arthritis, where prolonged inflammation and metabolic changes exacerbate the condition.[4]

LOA is not limited to older adults but can also affect younger individuals. In elderly patients, poor nutrition due to LOA can lead to compromised immunity, weight loss, and a heightened risk of infections. In children, LOA can impede growth and neurodevelopment. Studies suggest that a significant portion of patients with severe illnesses experience LOA, particularly those with a history of chronic health conditions.[2,3]

Effective management of LOA relies on early diagnosis and intervention. Tools like the CNAQ help healthcare providers assess and monitor appetite to predict potential weight loss. While appetite stimulants are available and can improve food intake and weight gain, they are often only prescribed after a patient has experienced significant weight loss. This delay in treatment highlights the need for better proactive management strategies.[3]

Increasing awareness among healthcare providers about the importance of early diagnosis and timely management of LOA is critical. Appetite-stimulating medications, including tonics, are commonly prescribed to address appetite loss and related conditions. Appetite regulation is influenced by multivitamins, amino acids and minerals, each playing distinct roles in modulating food intake.[5,6] Research indicates that multivitamin and mineral supplementation can reduce appetite. Lysine, an essential amino acid, has been shown to stimulate appetite by activating neuropeptide Y (NPY), a key regulator of food intake. Additionally, minerals and other nutrients in dietary compositions act on multiple biological pathways to enhance appetite control.[7]

The aim of this review is to explore the multifactorial causes, prevalence, and health consequences of LOA, while highlighting the importance of early diagnosis and timely management. It also examines various therapeutic interventions, including pharmacological treatments, to improve appetite and mitigate the adverse effects of LOA on patient outcomes.

EPIDEMIOLOGY AND DEMOGRAPHICS OF LOA

A multi-centre, cross-sectional survey conducted across India highlighted the significant burden of LOA among patients recovering from various health conditions. The study enrolled 15,914 participants, with a male predominance (63.5%) and a mean age of 38.5 years. Infectious diseases were the most common health disorders, affecting 68.7% of participants, with infections and infestation disorders being the most frequently observed condition (80.3%).[8]

LOA was highly prevalent, affecting 93.1% of the study participants. Among those with LOA, 33.8% had mild symptoms, 47.7% moderate, and 11.6% experienced severe to very severe appetite loss. Fatigue, a frequent co-occurring symptom, was observed in 91.1% of participants, with 44.4% reporting mild, 36.8% moderate, and 9.8% severe fatigue. The highest prevalence of LOA (93.8%) and fatigue (91.7%) was observed in participants with infectious diseases, particularly typhoid, which emerged as the leading cause of these symptoms.[5]

The survey also revealed important risk factors for LOA. Individuals with a past medical history had a 1.5 times greater risk of experiencing LOA, while participants with infectious diseases were 1.31 times more likely to report appetite loss ($p<0.0001$). Fatigue was more prevalent among participants older than 40 years (1.19 times) and those with a family history of medical conditions (1.27 times) ($p<0.0001$).[5]

Physician insights further emphasized the widespread nature of LOA. Over 95% of general physicians reported that patients experience appetite loss during both acute and chronic illnesses, with similar observations made by over 90% of consultant physicians. Paediatricians noted that nearly all paediatric patients experience LOA during acute illness, while over 90% suffer from LOA during chronic illness. Weakness and fatigue were commonly cited as presenting symptoms in conjunction with LOA.[3]

The Indian survey study on LOA during illness found that 93% of 15,914 participants reported LOA, with the highest prevalence in those with infectious diseases, particularly typhoid. The study also found that 91.1% of participants experienced fatigue, with those aged over 40 and with a medical family history at higher risk. This was the first pan-Indian study documenting the significant burden of LOA and fatigue in patients recovering from various health conditions.[8]

These findings underscore the need for increased awareness among healthcare providers regarding the diagnosis and management of LOA. Despite its high prevalence, many patients do not receive timely interventions to address appetite loss, leading to further complications. There is a pressing need for standardized guidelines to help physicians diagnose and manage LOA effectively, improving both the nutritional status and quality of life for affected patients.

AETIOLOGIES OF LOA

LOA can result from a variety of underlying conditions and processes, each contributing to disrupted hunger cues and nutritional imbalances. These factors can be broadly classified into physiological processes, medication effects, metabolic changes, and other complementary factors (Table 1).

Bacterial infections such as Salmonella, Campylobacter, and E. coli can cause gastrointestinal distress, leading to symptoms like diarrhea and abdominal cramps that result in short-term loss of appetite. Viral infections, including

Influenza, viral gastroenteritis, and Hepatitis A, also contribute to decreased appetite through systemic effects like fever, nausea, and fatigue. These infections highlight the body's response to illness, often manifesting as anorexia during acute phases.[9] Vitamin B12 and B1 deficiencies, particularly in the elderly, are associated with symptoms like loss of appetite, weight loss, and neurological issues.[10] These deficiencies are often linked to malnutrition and can be worsened by infections, which further impair nutrient absorption or increase metabolic demands. Loss of appetite is a common symptom in both vitamin B complex deficiencies, and the interplay between malnutrition and infections contributes to the exacerbation of these conditions.[11,12] Proper nutritional support is crucial in managing these cases.

Pathological processes

Several chronic health conditions are closely associated with LOA, particularly in diseases like cancer where anorexia/cachexia syndromes are prevalent. These physiological processes often lead to significant weight loss, malnutrition, and increased risks of morbidity and mortality. Cancer-related LOA, for example, is a result of complex metabolic disturbances and inflammatory responses that severely reduce food intake.[13]

Medication effects

Appetite suppression can also be an unintended consequence of certain medications. Drugs such as antimicrobials, including clindamycin and fluconazole, antihypertensive agents like thiazide diuretics, angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, and potassium-sparing diuretics, anti-diabetic drugs like biguanides, Sodium-glucose cotransporter-2 inhibitors and Glucagon-like peptide-1 receptor analogues, and chemotherapy are known to cause taste alterations or gastrointestinal discomfort, leading to reduced food intake. This iatrogenic LOA can exacerbate nutritional deficiencies, particularly in vulnerable patient populations who are already at risk.[6,14]

Metabolic changes

Appetite regulation involves the hypothalamus particularly the arcuate nucleus (ARC), brainstem, and peripheral signals to balance hunger, satiety, and energy homeostasis. Insulin regulates appetite by binding to insulin receptors in the hypothalamus, particularly in the arcuate nucleus. This activates the insulin receptor substrate proteins, which trigger the phosphatidylinositol-3-OH kinase pathway. This pathway reduces food intake and body weight, demonstrating insulins appetite-suppressing effects.[15]

Metabolic alterations seen in chronic diseases such as diabetes also contribute significantly to appetite regulation disruptions. Insulin resistance, for instance, is a common metabolic feature in these conditions, affecting how the body regulates hunger and nutrient absorption. Insulin itself has been shown to stimulate carbohydrate intake, potentially aiding in weight maintenance for patients struggling with LOA.[6]

Psychological factors

Psychological factors play a crucial role in the development of LOA. Emotional states such as depression, anxiety, and stress can diminish interest in food, while cognitive impairments may lead individuals to forget meals or lack motivation to prepare them. Furthermore, psychological conditions can reduce cravings for specific foods and disrupt the subjective sensations of hunger and satiety, making it difficult for individuals to recognize their nutritional needs. Overall, the complex interplay between mental health and appetite underscores the importance of addressing psychological issues to improve appetite and health outcomes in affected individuals.[5]

Concomitant factors

Other factors, including gastrointestinal disturbances, cognitive impairment, and swallowing difficulties (dysphagia), can further complicate appetite regulation. Gastrointestinal symptoms such as vomiting, stomatitis, or dietary restrictions during illness frequently contribute to diminished appetite. Some studies suggest that substances like ginger may positively impact gastric motility and stimulate hunger, underscoring the role of digestive health in appetite control. Fever, whether acute or prolonged, is another contributor to LOA, as sustained elevated body temperature can cause chronic weight loss due to prolonged appetite suppression.[6]

Coexisting symptoms and risk factors

There is a notable link between LOA and fatigue, highlighting that overall health and energy levels may directly influence an individual's appetite. Fatigue and reduced appetite often co-occur in patients with chronic illnesses, suggesting an overlap in the physiological pathways governing both conditions. Additionally, the presence of previous medical conditions and a family history of illness are known to increase the likelihood of LOA, indicating that both genetic predisposition and personal health history are critical factors in understanding its etiology.[5,6]

LOA during illness and its consequences

LOA in chronic illnesses is predominantly driven by systemic inflammation and hormonal imbalances. Proinflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), disrupt appetite-regulating circuits in the hypothalamus. Hormonal factors, including leptin resistance and altered levels of insulin and ghrelin, exacerbate anorexia in conditions like cancer and HIV. These illnesses often lead to cachexia, a metabolic syndrome characterized by

significant muscle loss, further reducing appetite and complicating energy balance. Psychological factors such as depression and anxiety compound these effects by impairing neural and hormonal appetite regulation.[4]

Table 1: Etiological factors of LOA.[5,6]

Category	Acute loss of appetite	Chronic loss of appetite
Pathological	Fever, acute infections (e.g., bacterial or viral gastroenteritis), nausea, stomatitis	Cancer (anorexia/cachexia syndrome), chronic gastrointestinal disorders, HIV
Drug-related	Side effects of antibiotics or antivirals	Long-term use of medications causing taste disturbances, chemotherapy
Metabolic	Acute metabolic changes due to infection or fever	Insulin resistance, chronic cachexia-related metabolic alterations
Genetic	-	Genetic predisposition to chronic appetite-affecting illnesses
Psychological	Stress, anxiety during acute illness	Long-term depression, psychological distress, cognitive impairment
Complementary	Vomiting, temporary dietary restrictions	Chronic gastrointestinal motility disorders, prolonged vomiting episodes

Table 2: Role of vitamin B12/B complex + Zinc + Lysine in the management of LOA.

Author/Study	Type of study	Outcome
Nagaraj et al[2]	Open-Label, Investigator-Initiated Study	The study showed a statistically significant improvement in mean CNAQ scores from baseline to weeks 1 and 2, indicating the effectiveness of the appetite-stimulating medication containing multivitamins, lysine, and zinc in improving appetite. No serious adverse events were reported, demonstrating the medication's safety for managing LOA.
Tiwaskar et al[3]	Cross-sectional, Questionnaire based Physician Survey	Nearly all patients with acute or chronic illnesses experience loss of appetite, along with weakness and fatigue. Many physicians view appetite-stimulating tonics as a suitable treatment option.
PMOS study[39]	Prospective, single arm, multi-centre, open label study	Appetite-stimulating syrup containing multivitamins, lysine, and zinc is effective for treating LOA in children and adolescents. Without any significant safety concerns.

Table 3: Comparison of Cyproheptadine and Vitamin B Complex (B3, B6, B12) + Lysine + zinc combination in the management of LOA.

Parameters	Cyproheptadine	Combination of Vitamin B complex (B3, B6, B12) + Lysine+ Zinc
Mechanism of action	Antihistamine and serotonin antagonist; stimulates appetite by blocking serotonin receptors.[20]	Utilizes multiple nutrients to stimulate appetite through various pathways, including orexigenic peptides and vagus nerve stimulation.[31-34]
Efficacy	Mild appetite stimulation; limited effectiveness in promoting weight gain.[40]	Proven to significantly improve appetite and nutritional status, particularly in LOA patients, by enhancing metabolism and nutrient absorption.[2,3,39]

Continued.

Parameters	Cyproheptadine	Combination of Vitamin B complex (B3, B6, B12) + Lysine+ Zinc
Safety	Generally favourable but with possible side effects such as drowsiness, dry mouth, and dizziness.	Safe, with minimal adverse effects reported, particularly in combination formulations; no serious adverse events in clinical trials.[3,3,39]
Combination advantages	Only addresses appetite stimulation via histamine and serotonin pathways.	Targets multiple mechanisms including energy production (B6, B12), appetite regulation (B3, Zinc), and nutrient absorption (Lysine), offering more comprehensive benefits for appetite and nutritional health

In chronic respiratory diseases like chronic obstructive pulmonary disease and pulmonary tuberculosis, inflammation and associated symptoms such as dyspnoea and swallowing dysfunction intensify appetite loss. Elevated levels of appetite-regulating hormones, such as peptide YY (PYY), have been observed in pulmonary tuberculosis, correlating with poor nutritional status. Similarly, chronic stress, mediated by prolonged glucocorticoid release, disrupts normal eating patterns and sensory-specific satiety, leading to a sustained decrease in food intake.[16-18]

Diabetes provides a unique perspective on appetite regulation, where destruction of pancreatic β-cells and altered secretion of amylin impair satiety signalling. Amylin, along with insulin and leptin, synergistically modulates food intake and gastric emptying. In type 2 diabetes, reduced ghrelin levels suppress hunger, while type 1 diabetes may exhibit paradoxically elevated ghrelin levels, further disrupting appetite regulation. Antihypertensive medications and comorbidities, including hypertension, contribute to appetite loss in the elderly, as shown in cross-sectional studies linking these conditions with depression, anxiety, and reduced food intake.[19]

The role of LOA in chronic diseases is evident in studies such as that by Nagraj et al, which analysed patients with a Council on Nutrition Appetite Questionnaire (CNAQ) score below 28, indicating decreased appetite. The study identified type 2 diabetes (44%) and hypertension (32%) as the most common comorbidities, particularly in the elderly. These conditions were often accompanied by psychological issues, such as depression and anxiety, which further disrupted appetite regulation.[2] Additionally, antihypertensive medications were implicated as potential contributors to LOA in elderly patients. Such findings underscore the multifactorial nature of LOA in chronic diseases, encompassing physical, psychological, and pharmacological factors.[20]

In contrast, acute illnesses like infections also elicit a significant inflammatory response, suppressing appetite through cytokine-mediated mechanisms. In conditions such as pneumonia, viral gastroenteritis, and malaria, cytokines like IL-1 and TNF-α act on hypothalamic circuits, inducing sickness behaviour and a fasting-like metabolic state. This response is often amplified by fever, increased metabolic demands, and psychological factors such as fatigue. Parasitic infections, such as malaria, further illustrate this interplay, where labile heme released during haemolysis exacerbates lethargy and appetite suppression. Conversely, pathogens like Salmonella Typhimurium may counteract this effect, as its effector protein SlrP blocks IL-1β signalling to the hypothalamus, enhancing host survival and facilitating bacterial transmission.[21-23] In a parasitic infection like malaria, illness-induced anorexia arises as a defence mechanism, reducing appetite and triggering sickness behaviour. Labile heme, a hemolysis byproduct, amplifies this effect by causing lethargy and further appetite suppression.[24]

Previous research has indicated that a reduction in appetite observed six months after intensive care unit (ICU) discharge may extend beyond this period, as suggested by comparisons with pre-ICU admission levels. Furthermore, a cohort study highlighted that individuals' post-ICU exhibited a lower appetite when compared to an age-matched healthy population.[25]

Stress can activate anorexigenic pathways, leading to a reduction in food intake, particularly when high-calorie, palatable foods are unavailable, resulting in stress-induced anorexia. During acute stress, catecholamines such as noradrenaline are released, which suppress appetite. The physiological response to acute stress, including increased heart rate, blood pressure, and reduced blood flow to the digestive system, further diminishes the desire to eat. Chronic stress, through the prolonged release of glucocorticoids, disrupts normal eating patterns and sensory-specific satiety, causing a sustained decrease in food intake.

Emotional stress also contributes to reduced food intake, supporting the link between stress and loss of appetite.[26] The role of cytokines in appetite regulation during both chronic and acute illnesses is intricate and involves chemical and neural mechanisms. For instance, cytokines such as TNF and IL-18 are released during infections like dengue and chikungunya, impacting areas of the brain like the Stria Terminalis, which directly affects appetite. Additionally, these cytokines stimulate adipose tissue to

release leptin, an appetite-suppressing hormone that also enhances immune cell activation. This shift towards a fasting-like state in the body optimizes immune function while limiting viral replication. These processes involve coordinated interactions between the immune, endocrine, and central nervous systems, regulating nutrient availability and consumption to support immune defence during illness.[27]

Effect of Loss of appetite on health

Prolonged anorexia, however, compromises host defence by weakening the immune response, increasing susceptibility to infections and heightening the risk of complications. Extended anorexia delays recovery by impairing the body's healing processes due to inadequate nutrition. While short-term anorexia may offer benefits, such as limiting viral replication, studies have shown that force-feeding infected animals decreases survival rates. Chronic anorexia, however, is linked to higher mortality, indicating its long-term detrimental effects. Additionally, prolonged anorexia can result in nutritional deficiencies, further compromising health and delaying recovery. These deficiencies can contribute to metabolic consequences, such as cachexia, where significant weight and muscle mass are lost due to chronic illness.[28]

It is acknowledged that poor nutritional status increases vulnerability to infections and can worsen their severity. In turn, serious or recurrent infections heighten the risk of malnutrition by causing anorexia and reducing nutrient intake, impairing nutrient absorption, or altering metabolism, which increases the body's nutrient demands. Therefore, ensuring sufficient levels of essential micronutrients is vital. A balanced diet is key to meeting the recommended intake of vitamins and minerals. However, even in developed countries, achieving the recommended daily allowance (RDA) of micronutrients can be challenging due to factors like reduced intake, heightened metabolic needs, and nutrient loss.[29] Appetite stimulation has been identified as a promising therapeutic approach, helping to enhance appetite, promote weight gain, and improve the overall quality of life for affected individuals.[5]

Pharmacological management of LOA

LOA is a significant clinical concern that can lead to substantial weight loss and nutritional deficiencies, ultimately affecting a patient's overall quality of life. Understanding the underlying conditions contributing to LOA is critical for developing appropriate management strategies. While various appetite-stimulating medications are available, their use is often initiated only after patients experience considerable weight loss and nutritional deficits, highlighting a gap in timely intervention. Effective management of LOA should focus on early identification and treatment, as appetite stimulation has been shown to be beneficial in improving appetite and promoting weight gain. Furthermore, a comprehensive understanding of the efficacy profiles of these medications concerning appetite and nutrition-related outcomes is essential for optimizing patient care. By addressing these gaps, healthcare providers can enhance the overall management of patients suffering from LOA, ensuring better health outcomes and improved quality of life.[2]

Corticosteroids are used to promote an appetite stimulation. However, they do not cause sustained weight gain. While effective as antiemetics, prolonged use can lead to side effects like hyperglycemia, immunosuppression, and Cushingoid syndrome, often requiring treatment discontinuation.[30]

Progestational agents like megestrol acetate are used to stimulate appetite and promote weight gain, particularly in cancer patients. Studies show they significantly improve appetite and weight gain compared to placebo. However, side effects such as fluid retention and hormonal imbalances may limit their use in some patients.[14] Medications like mirtazapine and olanzapine, used for psychiatric conditions, can stimulate appetite and help with weight gain in conditions like cachexia and cancer-related weight loss.

However, the potential side effects of these medications, including drowsiness, cognitive impairment, and psychological disturbances, along with the risk of dependence or addiction, may limit their use, particularly in children.[14] Eicosapentaenoic acid (EPA), an omega-3 fatty acid, has shown potential to stimulate appetite and prevent muscle wasting in cancer patients, though inconsistent research necessitates further investigation to confirm its benefits.[14]

Cyproheptadine, an antihistamine and serotonin antagonist, has been utilized for appetite stimulation. While it has demonstrated a mild stimulatory effect on appetite and possesses a relatively favourable safety profile, its effectiveness in promoting significant weight gain has been limited. Moreover, the use of cyproheptadine has declined in Favor of newer antihistamines that offer improved safety and efficacy profiles.[14]

In summary, a variety of pharmacological agents are available to stimulate appetite, but their use must be carefully considered, particularly in paediatric patients. Each agent carries its own set of advantages and limitations, including potential side effects and varying levels of efficacy in promoting weight gain.[14] The safety, tolerability, and effectiveness of appetite-stimulating medications are pivotal factors in selecting treatment for patients with LOA. A recent survey among consulting physicians and general practitioners in India revealed that 54% preferred multivitamin and multimineral-based appetite-stimulating medications, while 24% and 22% favoured antihistamine syrups and polyherbal formulations, respectively. Although medications like megestrol, dronabinol, and mirtazapine are associated with

adverse effects such as dizziness and nausea, megestrol poses a higher risk, particularly in hospitalized patients. In contrast, appetite-stimulating medications containing multivitamins, lysine, and zinc demonstrated no significant safety concerns, making them a suitable option for Indian patients.[2]

The combination of Vitamin B complex (B3, B6, B12), Lysine, and Zinc has been investigated as a promising approach to stimulate appetite and improve nutritional status. This blend utilizes the complementary actions of these nutrients to promote appetite and enhance overall health. Vitamin B6 and B12 are essential for metabolism and energy production, which may contribute to appetite stimulation by improving energy levels and overall well-being.[31] L-Lysine is a necessary building block for all proteins in the body. L-Lysine plays a major role in calcium absorption, building muscle protein, recovering from surgery or sports injuries and the body's production of hormones, enzymes, and antibodies.[32] For decades, lysine supplements have been extensively used to promote the growth and development of children.[33] Zinc, known for its role in stimulating food intake, acts on orexigenic peptides and the vagus nerve, particularly in individuals with zinc deficiency.[34]

Zinc plays a significant role in stimulating appetite by influencing the central nervous system, particularly via the afferent vagus nerve, a pathway crucial for regulating food intake during short-term zinc deficiency. When administered orally, zinc rapidly increases food intake, as observed in rats with early-stage zinc deficiency, by promoting the release of orexigenic peptides, which are hormones that induce hunger. Additionally, zinc sulphate administration enhances the expression of neuropeptide Y (NPY) and orexin mRNA, two neuropeptides involved in appetite and energy regulation. This appetite-stimulating effect is mediated by the vagus nerve, as studies in rats with severed Vagus nerves show that zinc does not increase appetite in the absence of this pathway, highlighting its essential role in zinc's mechanism of action.[34]

The zinc-lysine complex has been shown to improve zinc absorption, which is important for appetite regulation and overall nutritional health.[25] Lysine, an essential amino acid, aids in protein synthesis and improves the absorption of other nutrients, including zinc, thereby playing a supportive role in appetite stimulation.[35] Nicotinamide (Vitamin B3) supports metabolic processes and energy availability, which can further enhance appetite.[36] Vitamin B3, serves as an effective appetite stimulant, helping to increase the desire to eat and potentially leading to higher food intake.

This role of niacin in appetite regulation highlights its importance as a nutrient that supports healthy food consumption patterns.[37] Pyridoxine, or vitamin B6, is essential for appetite regulation, primarily by modulating appetite-regulating peptides in the hypothalamus and gastrointestinal tract. Its role in appetite control is closely linked to its influence on specific neuropeptides in both the brain and gut.[38]

A single-centre, open-label, single-arm study evaluated the efficacy and safety of an appetite-stimulating medication containing multivitamins, lysine, and zinc in Indian patients with a history of LOA. The study included 50 male and female outpatients (aged 18–55) diagnosed with LOA. Patients were administered 15 ml of the medication daily, and the change in CNAQ scores was assessed after two weeks of treatment.[2]

The mean patient age was 42.1 years, with 66% being male. Significant improvements in mean CNAQ scores were noted at week 1 (25.48±5.10) and week 2 (25.48±4.29) compared to baseline (22.08±2.76; $p \leq 0.0001$). Most patients had CNAQ scores of 17–28 at baseline, which was sustained in 66% at week 1 and 78% at week 2. In patients with acute and chronic illnesses, statistically significant improvements in CNAQ scores were observed. No serious adverse events occurred, indicating that the medication is a potentially effective and safe treatment option for managing LOA.[2]

Appetite-stimulating medications such as dronabinol, megestrol, and mirtazapine are commonly used for weight gain in outpatient settings, but their safety and effectiveness in Indian patients with LOA remain underexplored. This study found that a multivitamin-based appetite-stimulating medication containing vitamins B12, B3, B6, lysine, and zinc was a suitable and well-tolerated option for managing LOA in the Indian outpatient population. No significant safety concerns or serious adverse events leading to treatment discontinuation were observed.

Patients showed statistically significant improvement in CNAQ scores at weeks 1 and 2, demonstrating both effectiveness and high compliance (≥80%) with the prescribed regimen. The treatment duration is crucial for the efficacy of appetite-stimulating medications. Consistent with prior studies, a two-week therapy period yielded significant benefits in LOA management. While outpatient outcomes can vary due to factors such as medication adherence and timing, the results support the use of this multivitamin-based medication as an effective and safe treatment for Indian patients with LOA.[2]

Table 2 summarizes the various studies highlighting the role of combination of vitamin B complex + zinc + lysine in the management LOA.

Another prospective, multicentre, single-arm, open-label observation study evaluated effectiveness and safety of appetite-stimulating syrup (AST) containing multivitamins (vitamin B12, B3, B6) for managing LOA due to acute or chronic illness in children and adolescents. The primary endpoint of the study was the improvement in the child’s appetite, as reported by parents or guardians on

day 14 (±1 day), with appetite categorized as 0 (same as before) or 1 (improved compared to before). Secondary endpoints included the increase in meal quantity, based on the patient's food consumption compared to their usual intake, scored as 0 (less than usual), 1 (as usual), or 2 (improved).

Additionally, the mean change in meal frequency per day was assessed from baseline (day 0) to days 7 and 14 (±1 day). Physicians also provided a global assessment of effectiveness on Day 14 (±1 day). A total of 380 patients with a mean age of 10.0 (SD = 2.4) years were enrolled in the study. On day 14, 79.6% of patients reported an improvement in appetite. Additionally, 25.7% of patients reported significantly improved food consumption on day 7, with 79.6% reporting similar improvements by day 14.

The mean (SD) number of meals per day increased significantly, rising by 0.4 (SD = 0.6) meals (p=0.000) on day 7, and by 1.1 (SD=1.0) meals (p<0.001) on day 14. Investigators rated the effectiveness of AST as very good to excellent in 73.2% of patients, and good in 26.5%. Nine treatment-emergent adverse events (TEAEs) were reported in 9 patients (2.4%). Somnolence was the most common TEAE (1.6%), followed by diarrhoea, headache, and vomiting, each reported in 0.3% of patients.[39]

The table 3 provides a comparison between cyproheptadine and the combination of Vitamin B complex (B3, B6, B12), Lysine, and Zinc in the management of loss of appetite (LOA). It highlights key differences in their mechanisms of action, efficacy, safety profiles, and clinical outcomes based on available studies. This comparison underscores the potential advantages of the multi-nutrient combination in improving appetite and nutritional status, particularly in patients with LOA due to acute and chronic illnesses.

In summary, cyproheptadine and other pharmacological agents, including progestational agents like megestrol acetate, as well as polyherbal preparations, have demonstrated limited efficacy in significantly promoting weight gain and enhancing appetite. While cyproheptadine is recognized for its mild appetite-stimulating effects, its overall effectiveness in achieving substantial weight gain has been modest, leading to a decline in its use in Favor of newer medications with improved safety profiles.

Similarly, other appetite stimulants, such as mirtazapine and olanzapine, are associated with potential side effects that may limit their application, particularly in children. In contrast, the combination of Vitamin B complex (B3, B6, B12), lysine, and zinc presents distinct advantages for stimulating appetite and improving nutritional status. This multinutrient approach not only enhances appetite through various mechanisms but also supports metabolic processes crucial for energy production and overall health. Studies have shown that this combination effectively promotes weight gain and improves appetite without significant safety concerns. Vitamin B6 and B12 support energy production, nicotinamide (b3) aids in metabolic processes, lysine improves nutrient absorption, and Zinc directly acts on orexigenic peptides and the vagus nerve to stimulate food intake. The superior efficacy of this combination in improving appetite and nutritional status, as demonstrated in clinical studies, highlights its advantage over cyproheptadine, particularly in sustained appetite improvement and safety.

CONCLUSION

LOA is a widespread condition affecting patients across various age groups and health conditions. It can be short-term, caused by minor infections, or chronic, linked to serious illnesses like cancer, diabetes, and psychological factors. LOA contributes to malnutrition, weight loss, weakened immunity, and poor quality of life, particularly in elderly patients and children. Effective management of LOA requires early diagnosis and timely intervention to avoid further complications.

Tools such as the council on nutrition appetite questionnaire (CNAQ) are used to assess appetite, and pharmacological treatments like corticosteroids, progestational agents, and other appetite stimulants have been explored. While some medications show promise, their side effects often limit long-term use. A combination of multivitamins and zinc has been shown to be advantageous in stimulating appetite, supporting nutritional status, and enhancing immune function. This synergistic approach not only promotes better health in patients experiencing LOA but also serves as a valuable tool in addressing the complexities associated with appetite regulation. A timely management of LOA is crucial for improving patient outcomes and overall quality of life.

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