International Journal of Contemporary Pediatrics
Toshniwal A et al. Int J Contemp Pediatr. 2025 Jan;12(1):17-23
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20243777

Original Research Article

Effectiveness and safety of appetite-stimulating syrup in the management of pediatric patients with loss of appetite due to acute or chronic illness: results of a prospective, single-arm, multi-center and open-label study

Amarpal Toshniwal[1], Vinay Kumar Gill[2], Alka Parasher[3], Ankur Sethi[4], Rajib Kumar Ray[5], Avinash Ashok Sherkane[6], Milind Bhole[7]*, Ayndrila Biswas[7], Kartik Peethambaran[7], Pravin Namdeo Sawant[7]

[1]Vatsalya Children's Clinic, Bibwewadi, Pune, Maharashtra, India
[2]Department of Pediatric, Maharaja Agrasen Hospital, Jaipur, Rajasthan, India
[3]Department of Pediatric, Manglamplus Medicity, Mansarovar, Jaipur, Rajasthan, India
[4]Dr. Sethi Multispecialty Clinic, Noida, Uttar Pradesh, India
[5]Department of Pediatric, Sparsh Hospitals and Critical Care Pvt. Ltd., Bhubaneswar, Odisha, India
[6]Department of Pediatric, Abhayashasta Multispecialty Hospital, Bengaluru, Karnataka, India
[7]Department of Medical Affairs, Abbott Healthcare Private Limited, Bandra (E) Mumbai, Maharashtra, India

Received: 22 November 2024
Accepted: 07 December 2024

***Correspondence:**
Dr. Milind Bhole,
E-mail: Milind.bhole@abbott.com

ABSTRACT

Background: We evaluated the effectiveness and safety of appetite-stimulating syrup (AST) for managing loss of appetite (LOA) due to acute or chronic illness in Indian children and adolescents.
Methods: This was a prospective, multicenter, single-arm, open-label, observational study. Pediatric patients aged ≥6 to ≤15 years, with LOA due to acute or chronic illness were prescribed AST containing multivitamins (vitamins B12, B3, and B6), lysine, and zinc at a dose of 5 ml BID along with standard-of-care for 14 days.
Results: In all, 380 patients with a mean (SD) age of 10.0 (2.4) years were enrolled. Mean (SD) duration of LOA symptoms was 1.7 (1.2) months. Overall, 79.6% of patients reported improved appetite on day 14. Correspondingly, 25.7% and 79.6% patients reported statistically significant improvement in food consumption on days 7 and 14, respectively. The mean (SD) no. of meals per day improved significantly ($p<0.001$) to 2.9 (0.7) on day 7 and to 3.6 (0.8) on day 14, compared to 2.5 (0.5) meals per day at baseline. Investigators ranked the effectiveness of AST from very good to excellent in 73.2% and good in 26.5% of patients. No severe treatment-emergent adverse events were reported.
Conclusions: Two weeks of treatment with AST showed clinically relevant improvements in appetite and increased food consumption in children and adolescents with LOA due to acute or chronic illness. The syrup was ranked good to excellent for efficacy by investigators. These findings suggest that AST containing multivitamins, lysine, and zinc is effective for treating LOA in children and adolescents without any significant safety concerns.

Keywords: Loss of appetite, Appetite, Anorexia, Pediatric, Children

INTRODUCTION

Loss of appetite (LOA) is described as a loss or lack of desire to eat.[1] An adequate intake of food is important to meet the body's daily nutrition and energy requirements.[2] Prolonged LOA can cause significant weight loss and affect long-term nutrition, leading to weakness and fatigue, which can limit a person's daily activities.[1] In

children, inadequate food intake can lead to undernutrition, poor overall health, and inadequate growth. Moreover, LOA can compromise immunity leading to increased susceptibility to infections, which might become life-threatening, particularly in undernourished people.[3]

LOA can occur due to various reasons, including acute or chronic disease conditions, or might be caused by medications used for treating such conditions.[2] It is often a major concern for patients' families.[2] LOA might be brief and temporary, or prolonged and long-lasting. Acute LOA is usually temporary and is caused by illnesses such as benign viral or bacterial infections, while chronic LOA usually persists for a longer duration.[4]

Childhood is an age of higher nutritional requirements.[5] Acute illness in childhood is often associated with transient LOA.[6] Intermittent LOA is common in childhood, and can adversely affect a child's growth and development due to inadequate nutritional intake.[5] Prolonged LOA is associated with poor weight gain or loss of weight and is common in chronic illness.[6] Children in developing countries have a higher number of episodes of illness in a year than children of an identical age group in industrialized countries. Infection has an adverse effect on appetite and contributes to poor growth and a high prevalence of malnutrition in children of developing countries.[7] It has been previously shown that respiratory infections, diarrhoea, and fevers in children can suppress the appetite for several days each. Repeated illnesses in children have a cumulative negative effect on growth; it was reported that children with many days of LOA due to disease had poor gains in height and weight.[7] LOA can further lead to deficiency of nutrients, and affect quality of life.[8]

Appetite stimulation appears to be a beneficial treatment option for management of LOA. Various appetite-stimulating medications are available that can assist patients with LOA to improve appetite and gain weight, thereby, enhancing quality of life.[4] Various pharmacological agents have been investigated as appetite stimulants among adults; however, studies in pediatric patients are lacking. There is scarce Indian data on the use of appetite stimulants in pediatric and adolescent populations with a lack of prospective, clinical studies. The assessment of the effectiveness and safety of a drug is a continuous process to improve the quality and delivery of medical care. Hence, we aimed to evaluate the effectiveness and safety of AST in the management of Indian children and adolescents with LOA due to acute or chronic illness.

METHODS

Patients

This was a prospective, multicenter, single-arm, open-label, observational study (CTRI/2023/10/058301; date of registration 05 October 2023) to evaluate the effectiveness and safety of AST in the management of Indian pediatric patients with loss of appetite (LOA) due to any acute or chronic illness. Each 15 ml of AST (Betonin AST) contains Cyanocobalamin 5 mcg + Lysine HCL 100 mg + Nicotinamide 45 mg + Pyridoxine HCL 1.5 mg + Zinc sulfate 10 mg. This study was conducted from October 2023 to March 2024 at six sites across different geographical locations in India.

The inclusion criteria were male and female pediatric patients in the age group of ≥6 to ≤15 years, diagnosed with LOA due to any acute or chronic illness, prescribed Betonin AST syrup along with the standard of care for the acute or chronic illness, whose parents or legally acceptable representative (LAR) of pediatric patients could understand the study requirements and were willing to provide written informed consent for the child's participation. Additionally, patients in the age group of ≥7 to ≤11 years were asked to provide oral consent, and those in the age group of >11 to ≤15 years were asked to provide written consent for participation, in the presence of the parent or LAR (for patients in the age group of ≥6 to <7 years, parental consent was considered adequate).

The exclusion criteria were the patients taking ayurvedic/any other medications for the treatment of appetite loss for the past 2 months before the screening date, patients with a known history of hypersensitivity to any component of the study drug, patients with a known condition that according to investigators may interfere with the absorption or metabolism of study drugs. Additionally, patients with a known history of behavioural or psychiatric issues, and/or congenital heart disease, patients with any other conditions or diseases/medication that the investigator considered ineligible for enrolment in the study based on approved prescribing information, and patients with suspected inability or unwillingness to comply with study procedures, were excluded from the study.

Study design

The total duration of the study was 14 (±1) days. Enrolled pediatric patients were prescribed Betonin AST Syrup (as per the routine clinical practice and label) at a dose of 5ml twice daily, based on the clinical judgment of the investigator, for a period of 14 days post-enrolment into the study. Pediatric patients were followed up on day 7 and 14 (±1 day).

The study was conducted as per good clinical practices (GCP) and the new drugs and clinical trial rules, 2019, India to ensure that the rights, safety, and well-being of all participants were protected, and following the ethical principles in the declaration of Helsinki. The study protocol and the informed consent form were reviewed and approved by the ethics committee at each study site; before the initiation of the study. Parental consent and pediatric patients' assent to collect and use their medical

data were documented by the study staff before conducting any study-related assessment.

Study endpoints

The effectiveness was evaluated based on improvement in the clinical symptoms of LOA. The primary endpoint was the improvement in the child's appetite, as reported by parents/guardians (scored as 0: Same as before/ 1: Improved than before), on day 14 (±1 day). The secondary endpoints were an increase in the meal quantity, based on the quantity of food consumed by the patient compared with his or her previous intake (scored as 0: Less than usual/ 1: As usual, and 2: Improved), mean change in meal frequency per day, from baseline (Day 0) to day 7 and 14 (±1 day), patients' compliance to study medication and global assessment of effectiveness as rated by physicians and patients at day 14 (±1 day).

Safety endpoints included incidence of treatment-emergent adverse events (TEAEs), adverse drug reactions (ADR), Other pharmaceutical relevant information (OPRI), serious TEAEs and ADRs, and TEAEs and ADRs leading to treatment discontinuation throughout the study and global tolerability as assessed by physicians and patients on day 14 (±1 day).

Statistical analysis

With a sample size of 323 evaluable subjects required, a two-sided 95% confidence interval (CI) for a single percentage using the large sample normal approximation extended 5% from the observed percentage for an expected percentage of 70%. Assuming a 15% dropout rate study, 380 subjects were recruited to ensure 323 evaluable subjects at the end of the study.

All patients in the study who had taken at least one dose of study medication were included in the intention-to-treat (ITT) set. All patients in the ITT set who completed the study as per protocol were included in the per-protocol (PP) set and considered for effectiveness analysis. Categorical variables are presented as frequency (n) and percentages (%), compared using the Chi-square test at a 5% level of significance and the corresponding pvalue has been presented. The continuous variables are presented as mean, and standard deviation (SD). Paired t-test at a 5% level of significance was used to determine statistical significance in continuous variables. Data were analyzed using SPPS version 23 software.

RESULTS

Demographics and baseline characteristics

A total of 380 (193 male and 187 female) pediatric patients with a mean (SD) age of 10.0 (2.4) years were enrolled in the study. The mean (SD) duration of LOA symptoms was 1.7 (1.2) months. At baseline, the mean (SD) weight was 29.1 (8.4) kg. All patients had a history of medical conditions at the time of enrolment. Pyrexia (35.3%) followed by upper respiratory tract infection (21.1%), and common cold (8.7%) were the top three (3) ailments reported.

One (0.3%) patient was lost to follow-up and one (0.3%) patient was withdrawn from the study due to TEAE. Thus, 378 (99.5%) patients completed the study as per the protocol. The demographic and baseline characteristics of subjects are summarized in Table 1.

Table 1: Patient demographics and baseline characteristics-ITT population.

Parameters	Overall (n=380) (%)
Sex	
Male	193 (50.8)
Females	187 (49.2)
Age (in years), mean (SD)	10.0 (2.4)
Height (cm), mean (SD)	133.2 (14.5)
Weight (kg), mean (SD)	29.1 (8.4)
BMI (kg/m^2), mean (SD)	16.2 (3.0)
Duration of LOA symptoms (months), mean (SD)	1.7 (1.2)

Effectiveness of AST in pediatric patients with loss of appetite

Significant improvement in appetite was reported in 301 (79.6%) (95%CI 0.752 to 0.836; p<0.001) pediatric patients on day 14 (Table 2). At baseline 295 (78.0%) pediatric patients were consuming less than usual food, this figure declined to 74 (19.6%) and 3 (0.8%) on days 7 and 14, respectively. Correspondingly 97 (25.7%) and 301 (79.6%) patients reported improved food consumption on day 7 and 14, respectively. The change in food consumption pattern was evident from baseline to the end of the study in the per-protocol group. The food consumption pattern improved significantly among pediatric patients on day 7, (x^2[2, n=378]=23.510, p<0.001) and on day 14 (X^2[2, n=378]=19.048, p<0.001) (Figure 1).

Table 2: Improvement in the child's appetite at day 14 (per protocol population, n=378).

Parameters	N (%)
As usual	77 (20.4)
Improved	301 (79.6)
95% CI; p value (improvement in appetite)	(95% CI=0.752 to 0.836; p=0.000)$

$Analysed Using Clopper–Pearson (exact) test.

Compared to the baseline mean (SD) number of meals per day of 2.5 (0.5), the number of meals per day improved significantly by 0.4 (0.6) meals (95% CI=0.4 to 0.5; p=.000) at visit 2 (day 7±1), and by 1.1 (1.0) meals (95% CI=1.0 to 1.2; p<0.001) at visit 3 (day 14±1) (Figure 2).

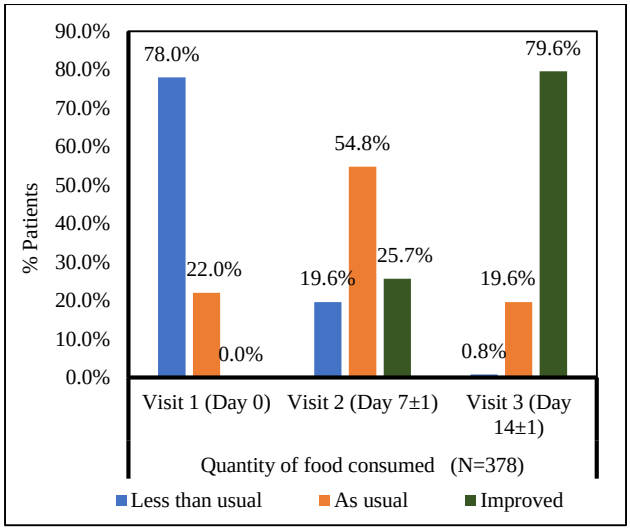

Figure 1: Assessment of quantity of food consumed by the child at days 7 and 14 (±1 day) (per protocol population, n=378).

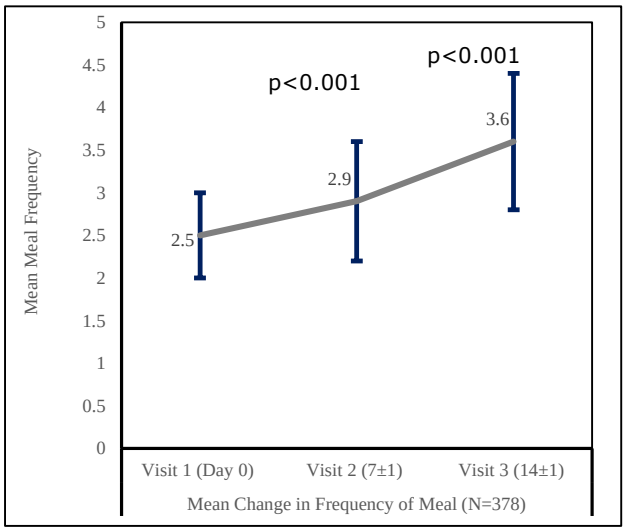

Figure 2: Mean (SD) change in frequency (number) of meals per day (per protocol population, n=378).

Patients missing <5% of doses of the study medication were categorized as compliant, those missing ≥5% to <15% of doses as moderately compliant, while patients missing ≥15% of the doses were categorized as non-compliant. The overall compliance with the study medication was overall satisfactory. On day 14, 90.7% of patients were reported to be compliant with the study treatment, and 7.7% and 1.6% respectively, were moderately compliant and non-compliant with the study treatment (Table 3).

The study investigators ranked the effectiveness of appetite stimulating syrup from very good to excellent in 73.2% of patients and good in 26.5% of patients. Similarly, 71.7% and 28.0% of patients described the effectiveness from "very good to excellent" and "good", respectively (Figure 3).

Table 3: Patients' compliance to study drug (PP, n=378).

Parameters	Visit 2 (day 7±1), N (%)	Visit 3 (day 14±1), N (%)
Compliant	348 (92.11)	343 (90.7)
Moderately compliant	29 (7.7)	29 (7.7)
Non-compliant	01 (0.3)	06 (1.6)

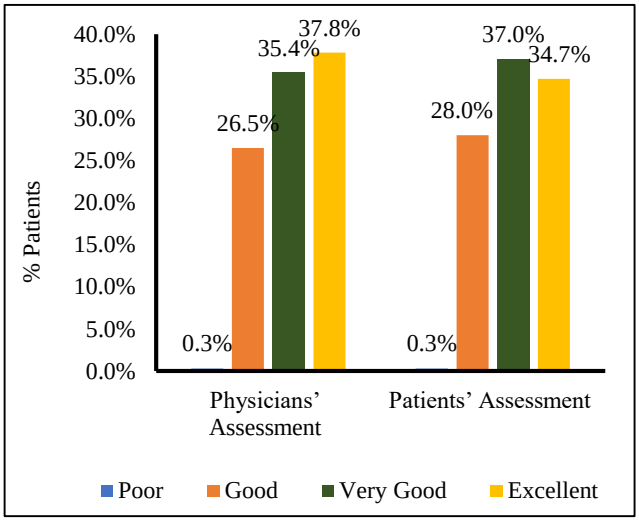

Figure 3: Global assessment of effectiveness by physician and patient (per protocol population, n=378).

Safety and tolerability

Nine TEAEs were reported in 9 (2.4%) patients. Somnolence (dizziness) (1.6%), followed by diarrhea, headache, and vomiting (0.3%) each, were the TEAEs reported.

All TEAEs were mild in nature; 3 (0.8%) TEAEs had possible, and 6 (1.8%) had no relationship to the study medication. In 1 (0.3%) patient, the study medication was discontinued and the patient was withdrawn from the study. No concomitant medication was prescribed and no action was taken on TEAE reported. All 9 TEAEs had resolved during the 14±1 day study period. No severe or serious TEAEs were reported (Table 4).

Table 4: Treatment-emergent adverse events by system organ class and preferred term-intent-to-treat population.

System organ class/preferred term	Total patients (n=380) (%)
Gastrointestinal disorders	02 (0.5)
Diarrhea	01 (0.3)
Vomiting	01 (0.3)
Nervous system disorder	07 (1.8)
Headache	01 (0.3)
Somnolence	06 (1.6)

Overall, the study drug was well-tolerated, with the study investigators reporting excellent tolerability in 47.1% of patients and very good tolerability in 25.4% of patients. Correspondingly, 46.3% and 25.7% of patients also described the tolerability of the study drug as excellent and very good, respectively (Figure 4).

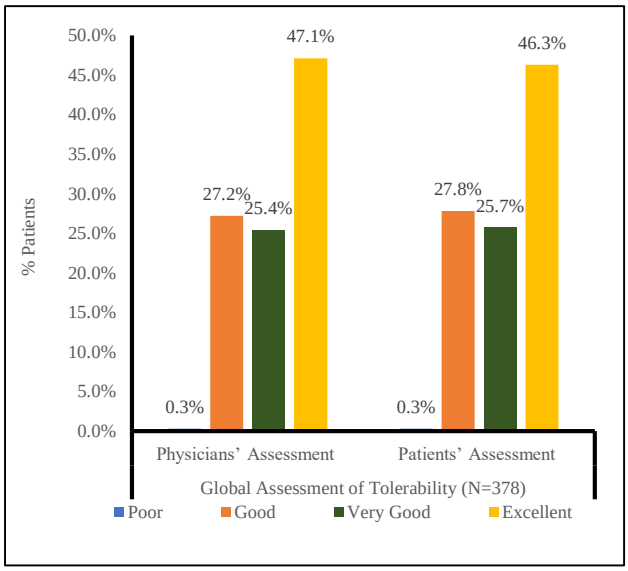

Figure 4: Global assessment of tolerability by physicians and patients (Per protocol population, n=378).

DISCUSSION

A transitory period of LOA is common following an acute illness. It can occur due to the disease itself or as an adverse effect of medications. Prolonged LOA can negatively affect immunity and delay recovery from infection. Prolonged LOA has also been shown to have a cumulative effect on children's growth with poor increases in height and weight. Chronic LOA can be considered as an indicator of the presence of the disease. Detecting and treating LOA before weight loss and nutritional deficiencies occur can prevent a decline in health.[7-9] LOA not only leads to nutritional deficiencies but can also occur due to nutritional deficiencies. Protein, iron, zinc, folic acid, and other B vitamins can lead to LOA and subsequent growth failure. LOA can occur due to diseases, infections, drugs, and abnormal hormones.[10] A study among Indian patients showed that up to 75% of subjects recovering from various disease conditions had mild or moderate LOA. The prevalence of LOA was high among patients with infections and infestations (94.40% and 91.1%, respectively).[8]

Our study showed that AST containing multivitamins, lysine, and zinc led to a significant improvement in appetite of the pediatric patients. An improvement in food consumption was seen in 25.7% and 79.6% of patients on day 7 and 14, respectively. Compared to the baseline mean number of meals per day, the number of meals per day also improved significantly on day 14.

Most patients in our study had pyrexia, upper respiratory tract infection, or common cold. A study among 525,643 adolescent girls, showed that infections treated with anti-infective agents were associated with an increased risk of a subsequent eating disorder.[11] Anorexia associated with infection is part of the host's acute phase response (APR), and is triggered by microbial products. The production of several cytokines during infection can induce anorexia and locally released cytokines can further reduce food intake.[12]

Poor appetite can also occur due to nutritional deficiencies; thus, LOA can be both a cause and a result of malnutrition. Lack of some micronutrients such as zinc, iron, and B vitamins can further decrease appetite. Children require macronutrients as well as micronutrients for growth. Therefore, administration of multiple micronutrients may be helpful in cases of LOA.[13]

Appetite stimulants such as megastore acetate (MA), cyproheptadine hydrochloride (CH), cannabinoids, anabolic and growth hormones, and serotonin have been used to treat LOA in children. However, many of these agents have considerable adverse effects.[5] In a recent survey among consulting physicians and general practitioners in India, 54% of the physician's preferred multivitamins and multimineral-containing appetite-stimulating medications for patients with LOA.[2] Appetite stimulating syrup (Betonin AST) contains minerals like zinc and lysine, and multivitamins like cyanocobalamin, nicotinamide, and pyridoxine. Humans require zinc for many physiological functions, such as growth, immune function, and reproduction.[14] It has been hypothesized that zinc may increase appetite and calorie intake.[15] In one study, appetite was reduced during experimental zinc deficiency and subsequently increased with its restoration.[16] Zinc is estimated to increase appetite through stimulation of the vagus nerve, which then stimulates the appetite center in the hypothalamus.[17] Moreover, it is reported that zinc-containing supplements contribute to the treatment of taste disorders caused by zinc deficiency.[18] A study reported that zinc supplementation alone can significantly increase the appetite and nutritional status of children.[17] Lysine is important for nutrition and development. It maintains bone health, enhances the immune system, helps in hormone production, and contributes to brain development. It plays a primary role in protein synthesis in the human body. However, dietary intake of lysine might be inadequate in those with LOA, since it is present in limited quantities in many essential food sources like grains. Inadequate intake of lysine leads to a greater risk of several adverse medical conditions in children and adolescents.[19] A previous study showed that the use of lysine as a supplement in the diet of prepubertal Indian girls increased their height, weight, and muscle strength.[20] Vitamin B12 deficiency in children can be difficult to diagnose as the presentation is often nonspecific, with symptoms such as developmental delay, irritability, weakness, and failure to thrive. The deficiency

can also lead to macrocytic anemia.[21] Vitamin B12 supplementation improves the metabolic profile and cognitive development in children.[22] Lack of vitamin B3 (nicotinamide) can lead to fatigue and loss of appetite.[23] Nicotinamide is essential for the growth and maintenance of the central nervous system, and its bioavailability is crucial for neuron survival and functions.[24,25] Vitamin B3 (pyridoxine) also performs various functions in the body and has an important role in cognitive development.[25] It is involved in gluconeogenesis and glycogenolysis in the body.[27] Its deficiency is often associated with microcytic anemia, and can cause irritability and convulsive seizures in infants.[26] Risk factors for deficiency of vitamin B6 levels include inadequate dietary intake. It is not stored in the human body; hence, a daily intake is necessary. This is particularly important in those consuming an exclusively plant-based diet and such people might benefit from supplementation.[27]

The direct effects of multi-vitamin supplementation in children have been assessed in several previous studies. Haskell et al investigated the effects of a single dose of multivitamin/ mineral supplementation on cognitive function in children. After 4 and 8 weeks, they noted improvements in performance in tasks related to attention.[28] Benton reported that children's non-verbal tests of intelligence improved with multivitamin supplementation.[29] Eilander et al in a meta-analysis reported a "marginal increase in fluid intelligence and academic performance in healthy schoolchildren".[30] A previous study from India showed that appetite-stimulating medication containing multivitamins, lysine, and zinc could be a suitable treatment option for the management of LOA in adults.[4] A combination of micronutrients can help improve the overall nutritional status of children. This approach ensures that various vitamin and mineral deficiencies are addressed, leading to better health outcomes. The synergistic effect of active ingredients cyanocobalamin (vitamin B 12), lysine, nicotinamide, pyridoxine, and zinc in AST can lead to enhanced bioavailability and improved nutrient absorption, potentially leading to a more pronounced effect on appetite.

To the best of our knowledge, this is the first of its kind study evaluating the effectiveness and safety of appetite-stimulating tonic in Indian pediatric patients with LOA.

There are certain limitations associated with our study. These include the open-label design, short follow-up period, and absence of a control and/or comparator group. We also did not monitor the weight at follow-up visits, which is a more objective parameter of improved food intake. Nevertheless, the sample size was statistically powered for drawing inferences from the study. Moreover, evaluation of the product in regular clinical practice offers the potential to bring research closer to practice.

CONCLUSION

The results of this prospective, multicentre, single-arm, open-label, observational study suggest that 14 days of treatment with AST containing multivitamins, lysine, and zinc produced clinically relevant improvements in the appetite and subsequent improvements in the frequency of meals in Indian pediatric patients with LOA due to acute or chronic illness. The AST (Betonin AST) was found to be an effective therapeutic option for the management of LOA in the pediatric population, with acceptable safety and tolerability profiles.

ACKNOWLEDGMENTS

Authors would like to thank to investigators and institutes associated with the study, CRO medONE Pharma solutions for support in conducting this study, and Dr. Sangeeta Dhanuka for writing support for the manuscript on behalf of medONE Pharma Solutions, Delhi, India.

Funding: Funding sources by Abbott Healthcare Pvt. Limited.
Conflict of interest: Kartik Peethambaran, Milind Bhole, Ayndrila Biswas, and Pravin Namdeo Sawant, are employees of Abbott Healthcare Private Limited and all remaining authors, Amarpal Toshniwal, Vinay Kumar Gill, Alka Parasher, Ankur Sethi, Rajib Kumar Ray and Avinash Ashok Sherkane received research grants from Abbott for participation in the study
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Gura K, Ciccone R. Drugs and Appetite. ICAN: Infant, Child, and Adolescent Nutrition. 2010;2(6):358-69.
2. Tiwaskar M. Perception, Approach and Management of Loss of Appetite: A Cross-sectional, Questionnaire based Physician Survey. J Assoc Physicians India. 2020;68(2):55-60.
3. Marathe D, Ratnakar P. A Survey to Assess the Efficacy and Tolerability of Natural Appetite Stimulants in Pediatric Patients. Indian J Clin Practice. 2023;34(3):10.
4. Nagaraj S. Loss of Appetite in Adult Patients: Effectiveness and Safety of an Appetite Stimulating Medication in an Open-Label, Investigator-Initiated Study in India. J Nutr Metab. 2022;2022:1-7.
5. Sastry J, Tathed PS, Rai RK, Sasibhushan V. Clinical Evaluation of Efficacy and Safety of Appetizer Syrup as Appetite Stimulant in Children with Non-Pathogenic Anorexia. 2017;16(4):700-5.
6. Adam HM. Loss of Appetite. Pediatric Care Online. 2020.
7. Pereira SM, Begumt A. The Influence of Illnesses on the Food Intake of Young Children. Int J Epidemiol. 1987;16(3):445-50.

8. Banerjee S, Vijayamohan M, Patel A, Singh S, Manjrekar P, Rathod R. Prevalence of Loss of Appetite in Patients Visiting Primary Care Physicians: A Cross-Sectional Survey. Indian J Med Sci. 2017;69(2):2-7.
9. Pilgrim AL, Robinson SM, Sayer AA, Roberts HC. An overview of appetite decline in older people. Nurs Older People. 2015;27(5):29-35.
10. Kazemi A, Rostami ZH, Akhlaghi M, Zahra M, Rostami H. Growth Faltering of Preschool-Aged Children with Poor Appetite Is Associated with Snacking Behaviors. J Health Sci Surveillance Sys. 2014;2(3):10.
11. Breithaupt L, Köhler-Forsberg O, Larsen JT, Benros ME, Thornton LM, Bulik CM, et al. Association of Exposure to Infections in Childhood With Risk of Eating Disorders in Adolescent Girls. JAMA Psychiatry. 2019;76(8):800.
12. Özen H, Kara A. Infection and Anorexia. Turk J Pediatr. 2006;48:279-87.
13. Hassanzadeh-Rostam Z, Kazemi A, Akhlaghi M. Effect of Multivitamin-Mineral Supplements Is Transient in Preschool Children With Low Appetite and Growth Failure. Infant Child Adolescent Nutrit. 2014;6(6):345-50.
14. Suzuki H, Asakawa A, Li BJ, Tsai M, Amitani H, Ohinata K, et al. Zinc as an Appetite Stimulator - The Possible Role of Zinc in the Progression of Diseases Such as Cachexia and Sarcopenia. Recent Patents Food Nutrit Agri. 2011;3(3):226-31.
15. Arsenault JE, López de Romaña D, Penny ME, Van Loan MD, Brown KH. Additional Zinc Delivered in a Liquid Supplement, but Not in a Fortified Porridge, Increased Fat-Free Mass Accrual among Young Peruvian Children with Mild-to-Moderate Stunting. J Nutr. 2008;138(1):108-14.
16. Shay NF, Mangian HF. Neurobiology of Zinc-Influenced Eating Behavior. J Nutr. 2000;130(5):1493S-9.
17. Kusumastuti AC, Ardiaria M, Hendrianingtyas M. Effect of Zinc and Iron Supplementation on Appetite, Nutritional Status and Intelligence Quotient in Young Children. Indones Biomed J. 2018;10(2):133-9.
18. Yagi T, Asakawa A, Ueda H, Ikeda S, Miyawaki S, Inui A. The Role of Zinc in the Treatment of Taste Disorders. Recent Pat Food Nutr Agric. 2013;5(1):44-51.
19. Gunarathne R, Guan X, Feng T, Zhao Y, Lu J. L-lysine dietary supplementation for childhood and adolescent growth: Promises and precautions. J Adv Res. 2024;S2090-1232(24)00202-9.
20. Verghese ST, Pauline M, Das A, Kurpad AV. Effect of 3-Month Lysine Supplementation on Growth and Muscle Function Parameters in Pre-pubertal Indian Girls. Indian J Nutr Diet. 2018;55(4):423.
21. Rasmussen SA, Fernhoff PM, Scanlon KS. Vitamin B12 deficiency in children and adolescents. J Pediatr. 2001;138(1):10-7.
22. Venkatramanan S, Armata IE, Strupp BJ, Finkelstein JL. Vitamin B-12 and Cognition in Children. Advances in Nutrition. 2016;7(5):879-88.
23. Maiese K, Chong ZZ, Hou J, Shang YC. The Vitamin Nicotinamide: Translating Nutrition into Clinical Care. Molecules. 2009;14(9):3446-85.
24. Fricker RA, Green EL, Jenkins SI, Griffin SM. The Influence of Nicotinamide on Health and Disease in the Central Nervous System. Int J Tryptophan Res. 2018;11:117864691877665.
25. Gasperi V, Sibilano M, Savini I, Catani MV. Niacin in the Central Nervous System: An Update of Biological Aspects and Clinical Applications. Int J Mol Sci. 2019;20(4):974.
26. NIH. Vitamin B6 Fact Sheet for Health Professionals. Recommended Intakes. Available at: https://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/#h2. Accessed on 14 August 2024.
27. Brown MJ, Ameer MA, Beier K, Brown MJ, Ameer MA, Daley SF. Vitamin B6 Deficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2024.
28. Haskell CF, Scholey AB, Jackson PA, Elliott JM, Defeyter MA, Greer J, et al. Cognitive and mood effects in healthy children during 12 weeks' supplementation with multi-vitamin/minerals. Brit J Nutrit. 2008;100(5):1086-96.
29. Benton D. Micro-nutrient supplementation and the intelligence of children. Neurosci Biobehav Rev. 2001;25(4):297-309.
30. Eilander A, Gera T, Sachdev HS, Transler C, van der Knaap HC, Kok FJ, et al. Multiple micronutrient supplementation for improving cognitive performance in children: systematic review of randomized controlled trials. Am J Clin Nutr. 2010;91(1):115-30.

Cite this article as: Toshniwal A, Gill VK, Parasher A, Sethi A, Ray RK, Sherkane AA, et al. Effectiveness and safety of appetite-stimulating syrup in the management of pediatric patients with loss of appetite due to acute or chronic illness: results of a prospective, single-arm, multi-center and open-label study. Int J Contemp Pediatr 2025;12:17-23.