NON-APPROVED INDICATION USE OF CYPROHEPTADINE AND ITS IMPLICATIONS FOR PATIENT SAFETY AND REGULATION

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ABSTRACT

Cancer related anorexia and cachexia significantly impair nutritional status, quality of life, and treatment outcomes. While appetite stimulants like megestrol acetate and dronabinol have shown effectiveness, their adverse effects limit long-term use. Cyproheptadine, a first-generation antihistamine and serotonin antagonist, has emerged as a potentially safer alternative. This review aims to evaluate critically synthesize previous research findingson clinical studies, randomized trials, and retrospective analyses on cyproheptadine's efficacy and safety as an appetite stimulant. It has shown consistent benefits across various populations, including children with cystic fibrosis, patients with nonorganic failure to thrive, and adults with cancer-related cachexia. Improvements include significant appetite score increases (e.g., K-ESAS change of –2.42 vs. –2.03 with placebo; p = 0.0307), average weight gains of ~24 g/day, and improved BMI and nutritional markers such as albumin and hemoglobin. The most common side effect was mild drowsiness, while serious adverse effects like hepatotoxicity were rare. However, concerns remain about off-label overuse in community settings, often due to lack of patient education and regulatory oversight. Overall, cyproheptadine appears to be an effective and well-tolerated short-term option for appetite stimulation. Nonetheless, more research is needed to establish long-term safety, efficacy, and appropriate dosing guidelines.

Keywords: Anorexia; Appetite stimulant; Cachexia; Cyproheptadine; Systematic review

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INTRODUCTION

Why do many cancer patients, despite undergoing proper treatment, still experience drastic weight loss and physical weakening? One of the main causes is cancer-related anorexia, a condition characterized by loss of appetite that leads to malnutrition, reduced quality of life, and suboptimal treatment outcomes (Fearon et al., 2011; Laviano & Koverech, 2020). Nutritional support is indeed important, but it is often not sufficient to overcome this loss of appetite. Therefore, efforts to find pharmacological solutions continue, one of which involves the use of cyproheptadine, an antihistamine and serotonin antagonist initially used for allergies, but also known to stimulate appetite. Anorexia and cancer-associated cachexia syndrome (CACS) are conditions frequently experienced by cancer patients, particularly in advanced stages, and they significantly contribute to the deterioration of clinical condition and life expectancy. (Soliman et al., 2021). Unfortunately, effective treatment options remain limited to this day.

The use of cyproheptadine as an appetite stimulant may offer a potential solution to address anorexia and cachexia in cancer patients. However, since the primary function of cyproheptadine is as an antihistamine and serotonin antagonist, its effectiveness in stimulating appetite is still not clearly established. In addition, it is important to determine the appropriate dosage and frequency of cyproheptadine use, as well as its side effects, to ensure its safety as an appetite stimulant (Hassan et al., 2024). As a follow-up, this study was conducted with the aim of producing a journal review that provides a comprehensive and structured overview of cyproheptadine use as an appetite stimulant for patients with anorexia and cachexia syndrome. Through this study, it is hoped that the findings will serve as a valuable evidence-based reference for decision-making regarding the use of cyproheptadine as an appetite stimulant.

MATERIALS AND METHODS

This research is a literature review that focuses on the analysis of articles, namely off-labeled drugs on Siproheptadin for appetite stimulants. The method used in this preparation is Literature Review which is sourced from PubMed, Google Scholar and Science Direct. Search keywords in the reviewed article are Cyproheptadine,Off-label use OR Off-label drugs,Appetite Stimulants,Serotonin Antagonists,Histamine H1 Antagonists. The selected article must meet several criteria, namely does not include review article, book chapter, letter to editor, conference abstract, case study, thesis/desertion, guidelines and journal publication year under 10 years. After going through several stages of matching with the criteria that want to be researched, there are 9 articles, namely in pubmed 3, google schoolar 6 that are eligible for review

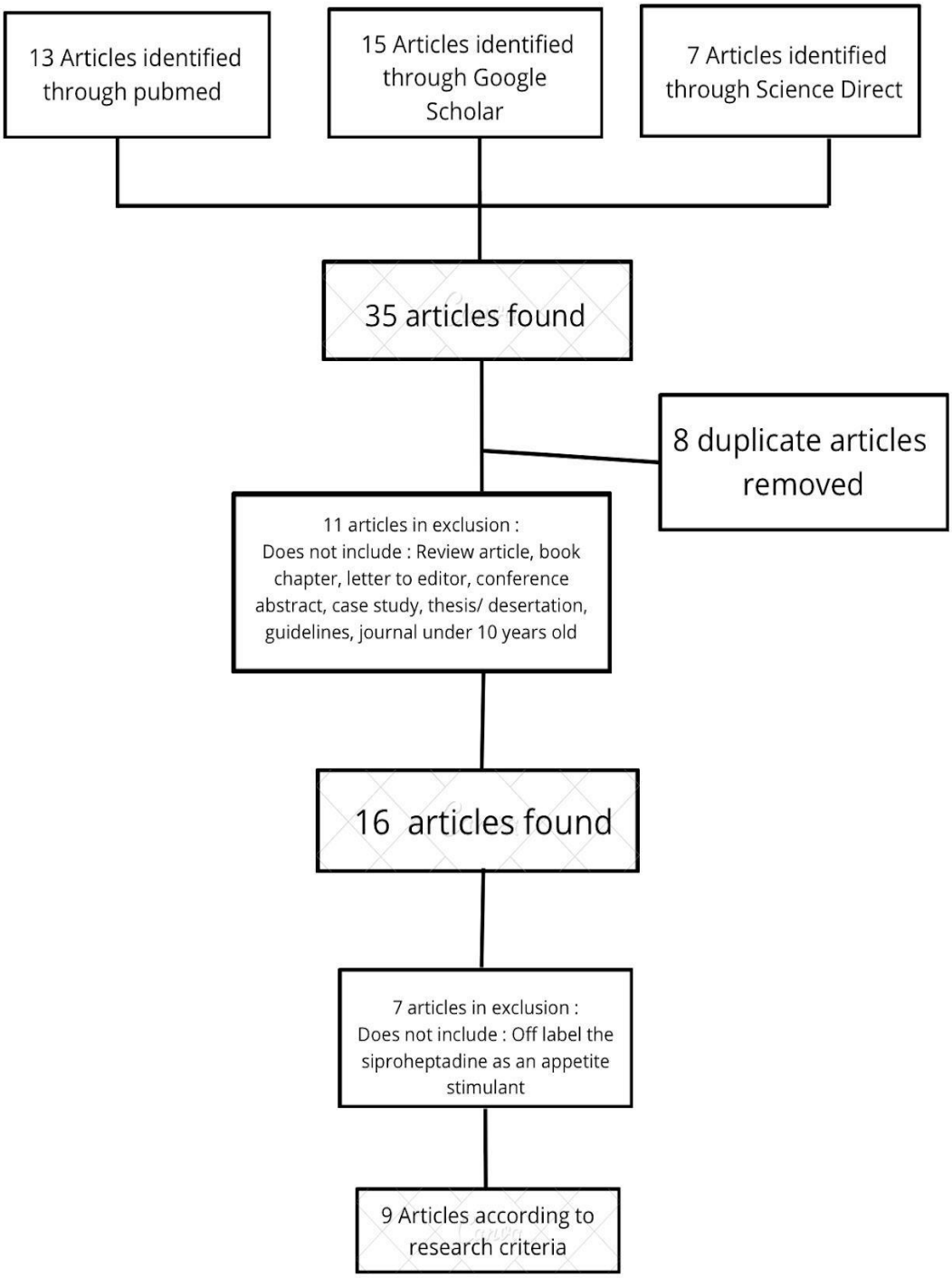

Figure 1. Prism Flow Chart

RESULT

Table 1. Article Review Result

Authors	Location	Title	Methods	Results
Mayank Gupta, Nihit Gupta, Jayakrishna Madabushi.	USA	Off-Label Cyproheptadine in Children and Adolescents: Psychiatric Comorbidities, Interacting Variables, Safety, and Risks of Hepatotoxicity.	Case report.	Cyproheptadine was associated with elevated liver enzymes (AST: 70 U/L; ALT: 85 U/L) in an adolescent using it for migraine and appetite stimulation. Following drug discontinuation and the initiation of treatment for anxiety, symptoms significantly improved without the need to resume cyproheptadine. This highlights the importance of addressing underlying psychiatric conditions, which may reduce the need for pharmacological intervention, as well as the necessity of monitoring hepatic side effects.
Sue Youn Kim, Jae Moon Yun, Ji-Won Lee, Young Gyu Cho, Kyung-Hwan Cho, Yong Gyu Park, and Belong Cho.	South Korea	Efficacy and Tolerability of Cyproheptadine in Poor Appetite: A Multicenter, Randomized, Double-blind, Placebo-controlled Study.	Randomized, double-blind, placebo-controlled clinical trial.	Cyproheptadine significantly increased appetite, as evidenced by a mean change in K-ESAS appetite scores of –2.42 compared to –2.03 in the placebo group (statistically significant difference, $p = 0.0307$). Weight gain was also greater in the cyproheptadine group, with an increase of +0.37 kg at week 8, compared to a decrease of –0.10 kg in the placebo group ($p = 0.0098$). BMI increased by +0.14 kg/m² in the cyproheptadine group ($p = 0.0040$) after 8 weeks. The most commonly reported side effect was drowsiness, which was generally mild and well tolerated. These findings support the safety and efficacy of cyproheptadine compared to placebo.
Jodi Grunert, Natalie van der Haak, Carol La Vanda, Nigel Farrow, and Andrew Tai.	Australia	Cyproheptadine as an appetite stimulant in children with cystic fibrosis.	Retrospective chart review	Children with cystic fibrosis who received cyproheptadine for 12 months showed a significant improvement in nutritional status, as indicated by an increase in z-BMI scores from –1.06 to –0.15 (mean increase of +0.91; $p < 0.0001$). In comparison, during the 12 months prior to treatment, the z-BMI score had decreased by –0.52, indicating a positive effect of cyproheptadine on

				nutritional status. No correlation was found between the dose and BMI improvement, and reported side effects were mild, primarily drowsiness.
Yasser H. Hassan, Nasser M. Abdelbary, Suzan A. Alhassanin, Mohamed E. Ahmed, Suzy F. Gohar	Menoufia University, Egypt	Role of Cyproheptadine as Appetite Stimulant in Cancer Associated Anorexia	Randomized controlled clinical study	The results showed that cyproheptadine administration in cancer patients with anorexia and cachexia showed no improvement in appetite scores compared to the control group, but showed protective effects on weight loss, body mass index (BMI), albumin and hemoglobin levels, and quality of life (FAACT) scores during the 12-month follow-up period. Although there was no significant difference between the two groups at baseline, the control group experienced a decline in nutritional parameters and quality of life, while the drug group remained relatively stable, indicating cyproheptadine has potential in maintaining the nutritional status and general condition of patients. Regression analysis showed that baseline ESAS score, performance status, and albumin levels were the main factors influencing appetite. Minimal side effects were reported, with somnolence in 7.2% of patients, indicating that cyproheptadine is safe to use.
Sirasit Chansane, Woranat Suntornsantoon, Pongpan Chaiyapak, Daylia Thet, dan Tippawan Siritientong	Thailand	A Retrospective Study of Body Weight Changes in Patients Receiving Cyproheptadine in A Hospital-Based Outpatient Setting in Thailand	Retrospective longitudinal study	The results showed cyproheptadine was given as an off-label drug to stimulate appetite and promote weight gain, especially in patients with medical conditions such as hypertension, dyslipidemia, and diabetes mellitus. More than 80% of participants experienced polypharmacy. All patients were taking a 4 mg dose of cyproheptadine per day, usually at night due to its sedative effect. Analysis showed no significant change in weight or body mass index between the first and second visit, with an average interval of

				6 months. Advanced age and high HDL levels were found to be negatively correlated with weight. Patients with abnormal body weight tended to take more medication, have high blood pressure and high LDL levels.
Seyed Alinaghi Kazemi, Maedeh Khosravi Yekta, Ramazan Fallah, Diana Noemi Diaz, Kambiz Eftekhari.	Ayatollah Mousavi Hospital, Zanjan, Iran	Evaluation of Cyproheptadine Hydrochloride Effects on Weight Gain in Underweight Children with Anorexia; A Randomized Clinical Trial	Randomized Clinical Trial with double-blind design	Results showed that the mean weight gain in the cyproheptadine group was significantly higher than the placebo group (1.08 ± 0.67 kg vs. 0.22 ± 0.46 kg; $p=0.005$). The increase in height was also greater in the cyproheptadine group (1.60 ± 0.97 cm vs. 0.86 ± 0.85 cm; $p=0.005$). In addition, 100% of children in the cyproheptadine group experienced improvement in appetite, compared to 52.7% in the placebo group. No serious side effects were found during the use of cyproheptadine.
Mustafa Alssageer, Ali Alsahref, Mokter Abdelqader.	Community pharmacies in Sebha City, Libya	Characteristics, Perspectives, and Experiences of Cyproheptadine Users at Community Pharmacies in the Context to Prescription Medication Misuse	Descriptive Cross-sectional	The results showed that most respondents (96.1%) purchased cyproheptadine from community pharmacies, and the majority (76.7%) obtained it without a prescription. The main reasons for using the drug were to increase appetite (51.5%), gain weight (24.3%), and improve body shape (18.4%). However, most respondents did not know the other uses of these drugs (69.9%) or their side effects (59.2%). The main source of information came from friends or family (33%), followed by pharmacists (28.2%) and doctors (17.5%). The most common effects felt during use were drowsiness (68.2%) and weight gain (20.1%). About 45.6% of respondents were satisfied with the results of using the drug, and almost half of them suggested its use to others, although most were unaware of the risks or warnings associated with the drug.
Yi-Chun Lin, Hung-Rong	China Medical	Effects of cyproheptadine	A Retrospectiv	Of the 788 children analyzed, no significant difference in age-adjusted

Yen, Fuu-Jen Tsai, Chung-Hsing Wang, Lung-Chang Chien, An-Chyi Chen, Ro-Ting Lin.	University Hospital, Taichung, Taiwan	on body weight gain in children with nonorganic failure to thrive in Taiwan: A hospital-based retrospective study	e Study	body weight was found between the cyproheptadine group and the control group during follow-up. However, in the group receiving cyproheptadine, the longer the duration of drug use, the greater the increase in weight and BMI, with a statistically significant association. Each additional day of cyproheptadine use increased body weight by an average of 26.45 grams per day. This effect of increased weight and BMI was also more pronounced in younger children. This study concludes that the use of cyproheptadine may help to gradually increase weight and BMI in children with nonorganic FTT, especially when used over a long enough period of time, although further prospective studies are needed to confirm its benefits and safety in the long term.
Mohammad Reza Mohammadi, Seyed-Ali Mostafavi, Payam Hosseinzade, Mandana Nojoumi and Fatemeh Asadian-Koohestani.	Psychiatry & Psychology Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Iran	Comparing the Effects of Folic Acid and Cyproheptadine on Appetite, Weight, and ADHD Symptoms in Children with ADHD: A Randomized Clinical Trial	Randomized Clinical Trial with double-blind design	Of the initial 56 participants, 47 children completed the study (23 in the folic acid group, 24 in the cyproheptadine group). Results showed that folic acid was significantly more effective in reducing hyperactivity symptoms than cyproheptadine ($p=0.035$), although there were no significant differences in attention scores, sleep disturbance, or general weight change. However, girls who received folic acid showed greater weight gain than the other groups. Height gains were also more pronounced in girls in both groups, but were not significant between groups.

DISCUSSION

Cancer patients are at high risk of malnutrition due to both tumor-related effects and treatment side effects that reduce appetite. While appetite stimulants such as megestrol acetate and dronabinol have been shown to improve appetite, their use is limited due to serious adverse effects. Therefore, safer alternatives are needed. Cyproheptadine, a first-generation antihistamine, is known to increase appetite and body weight, and is frequently used in pediatric populations. Its appetite-stimulating and weight-gaining effects are likely mediated by its antiserotonin activity on the hypothalamic feeding center (Kim et al., 2021).

Studies in adult cancer patients with anorexia have shown that cyproheptadine significantly improves appetite scores, body weight, BMI, and hemoglobin levels, although factors such as functional status and disease stage remain more dominant in determining nutritional status (Gupta et al., 2023). In children with cystic fibrosis (CF) and malnutrition, cyproheptadine has also been proven to increase BMI-z scores and showed a trend toward improved pulmonary function, even at low doses administered twice daily, without a clear dose-response relationship (Homnick et al., 2004). Another study involving underweight children aged 2–10 years reported significant increases in both weight and height within two months of cyproheptadine intervention compared to placebo, with minimal side effects such as drowsiness (Najib et al., 2014; Rerksuppaphol & Rerksuppaphol, 2010). Compared to megestrol acetate, cyproheptadine is considered safer and more effective due to the absence of serious side effects such as adrenal suppression or glucose metabolism disturbances (Couluris et al., 2008).

On the other hand, off-label use of cyproheptadine in the general population, particularly in developing countries such as Libya, reveals a concerning trend. Studies show that the majority of users are young, unmarried women who consume the drug to enhance body shape and self-image—strongly influenced by cultural and social pressures that associate a heavier body with attractiveness, health, or affluence (WHO/EMRO, 1989; Saleh, 2012).

Most users obtain the drug without a prescription and lack adequate education regarding side effects and dosage. Information is often acquired from friends or family rather than healthcare professionals. Moreover, drug advertisements featuring images of fruits have been shown to influence public perception, leading to excessive and uncontrolled consumption. In fact, unsupervised use of cyproheptadine may lead to serious adverse events, including hallucinations, seizures, central nervous system depression, and sudden cardiac arrest in cases of overdose.

Although most users report satisfaction with the results of cyproheptadine use, the low involvement of pharmacists and pharmaceutical personnel in providing information and supervision highlights weaknesses in community drug control systems. Therefore, despite its proven effectiveness in specific medical contexts, the use of cyproheptadine requires strict supervision, adequate public education, clear sales regulations, and strengthened roles of pharmacists to prevent misuse and adverse health impacts. Thus, although cyproheptadine shows promise as an effective weight-gain agent, its use must be based on appropriate medical indications and under the guidance of qualified healthcare professionals.

CONCLUSION

The off-label use of cyproheptadine originally intended to treat anorexia and cachexia in cancer patients as an appetite stimulant has gained increasing attention in recent years. Various reviews have demonstrated that cyproheptadine significantly enhances appetite. Clinical evaluations indicate that patients receiving cyproheptadine experienced an average weight gain of approximately 24.45 grams per day. Moreover, prolonged administration of cyproheptadine has been associated with greater improvements in both body weight and body mass index (BMI). Compared to several other appetite-stimulating agents, cyproheptadine appears to have a higher potential to promote weight gain. However, when compared to folic acid, the weight gain associated with cyproheptadine is reportedly lower. The longest recorded duration of cyproheptadine use in the literature

is 12 months, during which patients maintained relatively stable nutritional parameters and quality of life suggesting that cyproheptadine may contribute to the long-term maintenance of nutritional status and overall well-being. Although cyproheptadine does cause side effects, they are generally mild, with drowsiness being the most commonly reported. Overall, the use of cyproheptadine as an appetite stimulant has proven to be effective in promoting meaningful weight gain in patients. Nevertheless, further studies are warranted to fully assess the long-term safety and efficacy of this medication.

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