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# APPETITE STIMULANTS: INSIGHTS INTO PHARMACOLOGICAL INTERVENTIONS

**Mohammed Rizwana *, Syeda Nishat Fathima**

Department of Pharmacology, Jayamukhi College of Pharmacy, Narsampet, Warangal-506332, Telangana, India

Email: mohammadrizwaana@gmail.com

**ABSTRACT:**

Chronic and acute illnesses can impact patients' appetite and weight, potentially leading to cachexia. Although these changes typically progress over weeks to months, acutely ill patients may experience a loss of appetite and subsequent weight loss in a shorter period, potentially causing further complications like severe anorexia, cachexia, depression, and increased infection risk. These complications may necessitate additional therapies and longer hospital stays. Therapy should focus on preventing further weight loss or facilitating weight gain, especially in aging patients and those with psychological disorders, malignancy, chronic infections, and other chronic disease states. Unintentional weight loss, defined as 5% of body weight in a month or 10% in a 6-month period, may occur more rapidly in acutely ill patients. Medications like dronabinol, megestrol, and mirtazapine can help patients improve appetite and gain weight over weeks to months.

**Keywords:** Appetite; Orexigenic; Dronabinol; Megestrol; Mirtazapine

## INTRODUCTION:

Appetite is the desire to eat food, often triggered by hunger/ Satiety. It exists in all life forms and regulates energy intake to meet metabolic needs. It is regulated by a close interplay between the digestive tract, adipose tissue and the brain. An orexigenic, or appetite stimulant, is a drug, hormone, or compound that increases appetite and may induce hyperphagia. Appetite enhancement, often a side effect of certain drugs, can be beneficial in patients suffering from severe appetite loss or muscle wasting [1]

Food intake is influenced by metabolic, gastrointestinal, and sensory signals. Taste, odour, and texture can affect a patient's motivation to eat, and dietary preferences are often influenced by previous feeding experiences. Mastication, distension of the gastrointestinal tract,

and postabsorptive changes in nutrient levels stimulate hormones that control food intake. Dopamine release, which stimulates food intake, and cholecystokinin release, which inhibits appetite, are examples of these neurotransmitters. Other neurotransmitters like catecholamines, serotonin, and GABA also play physiological roles in food intake control. The brain regulates appetite through hormonal and neuronal pathways, influenced by both internal and external stimuli. Key sites for controlling hunger and satiety include the hypothalamus and parabranchial nucleus. Although the complexity of appetite regulation makes it challenging to control all components, it offers opportunities to manipulate appetite through external environmental and palatability factors, as well as pharmacological support of hunger cues. [2]

**MECHANISM OF APPETITE STIMULATION:**

Understanding feeding mechanisms is crucial for understanding therapeutic approaches. While increasing food intake may compensate for weight loss, it may still cause a shift in tissue distribution, especially in muscle loss. The two distinct subsets of neurons that control food intake are the neurons that produce neuropeptide Y (NPY), which stimulate feeding, and melanocortin peptides, which act as inhibitors of eating. Typically, when one of these neurons are activated, the other is inhibited. Whilst circulating leptin and insulin decrease appetite by inhibition of NPY- or agouti-related peptide (AgRP), melanocortin-producing neurons in the arcuate nucleus region of the hypothalamus stimulate it. During weight loss NPY expressing neurons are activated, and melanocortin-producing neurons are inhibited, which are responses that stimulate eating and promote the recovery of depleted stores until sufficient food becomes available. Ghrelin activates NPY and AgRP thus yielding stimulation of food intake. [3]

The leptin gene, a hormone derived from adipose tissue, is crucial in identifying neural pathways and neuropeptides controlling body weight. Leptin stimulates neural circuits that decrease food intake and increase energy expenditure. The arcuate nucleus of the hypothalamus is a crucial relay center for leptin's effects. It integrates and distributes peripheral information from hormonal and neural signals, reflecting metabolic status, into the brain. Within the arcuate nucleus, neurons containing melanocortins (MCs), products of the pro-opiomelanocortin (POMC) gene, are activated by leptin. Fasting leads to loss of adipose tissue and low leptin levels, while overfeeding stimulates POMC neurons. POMC neurons are stimulated during a positive energy balance, and increased plasma leptin levels contribute to this stimulation. The

melanocortin system's activity is regulated by both endogenous melanocortin receptor agonists, α-melanocyte-stimulating hormone, β-MSH, and γ-MSH, and agouti-related protein (AgRP). AgRP is expressed in the arcuate nucleus but in a different subset of neurons than those expressing POMC. AgRP neurons are inhibited by leptin and activated during negative energy balance. AgRP acts as an inverse agonist on constitutively active MC3 and MC4 receptors, the main brain MC receptors. This tight regulation of MC function in the brain suggests that AgRP neurons are activated during a negative energy balance, suppressing MC receptor activity. [4]

**THERAPEUTIC USES OF APPETITE STIMULANTS:**

- AIDS-associated anorexia, cachexia, or weight loss
- Nutritional Management in Peritoneal Dialysis
- Prevent weight loss/promote weight gain
- Preoperative and postoperative nutrition in hepatobiliary surgery
- Anorexia of non-AIDS-related etiology or require appetite stimulation
- Appetite stimulation or relief from nausea/vomiting associated with a comorbid cancer diagnosis
- Severe anorexia nervosa.
- Muscle wasting due to cystic fibrosis, old age and cancer

**LIST OF OREXIGENICS:**

- 5-HT2C receptor antagonists/inverse agonists — mirtazapine, olanzapine, quetiapine, amitriptyline, cyproheptadine, lurasidone
- H1 receptor antagonists/inverse agonists — mirtazapine, olanzapine, quetiapine, amitriptyline, cyproheptadine, pizotifen
- Dopamine antagonists — haloperidol, chlorpromazine, olanzapine, risperidone, quetiapine
- Adrenergic antagonists:

  β blockers — propranolol, etc.

  α2 adrenergic antagonists— mirtazapine, mianserin

  Mixed α1/β blockers — carvedilol
- CB1 receptor agonists (cannabinoids — THC/dronabinol (a component of Cannabis), nabilone
- Corticosteroids — dexamethasone, prednisone, hydrocortisone

- Anabolic steroids — oxandrolone, boldenone undecylenate, testosterone
- Certain pregnene steroids — megestrol acetate, medroxyprogesterone acetate
- Sulfonylurea antidiabetic drugs such as glibenclamide, chlorpropamide and tolbutamide
- Ghrelin receptor agonists such as anamorelin, GHRP-6, ibutamoren, ipamorelin, and pralmorelin
- Sugars, such as fructose
- Alcohol beverages
- Benzodiazepines, such as diazepam
- Mood stabilizers such as lithium
- Insulin

**MECHANISM OF APPETITE SUPPRESSION BY DRUGS:**

**Megestrol acetate:** Megestrol acetate is approved for the management of anorexia, cachexia, or unexplained weight loss associated with AIDS. Although the mechanism of action is unknown, megestrol acetate may enhance appetite stimulation by antagonizing the metabolic effects of catabolic cytokines. Megestrol acetate is thought to derive its orexigenic effects by increasing Neuropeptide Y production in the hypothalamus, though this leads to a gain primarily in fat mass and little advantage in lean mass retention. Megestrol acetate induces a variety of downstream changes to cause the orexigenic effect, including stimulation of neurosteroid-like modulation of calcium channels in the ventromedial hypothalamus and inhibition of the secretion of proinflammatory cytokines including interleukin 1α, interleukin 1β, interleukin 6, and tumor necrosis factor α, all of which have been implicated in facilitation of appetite. Increased levels of insulin-like growth factor 1 (IGF-1) may also be involved, specifically in its anabolic effects. [5]

**Mirtazapine:**

Mirtazapine is an atypical antidepressant, a serotonergic norepinephrine uptake inhibitor and is used primarily for the treatment of a major depressive disorder. it has been shown that blockage of pancreatic β cell α2-adrenoceptors with various substances disinhibits insulin secretion and reduces glucagon secretion, both decreasing blood glucose. The net increase in norepinephrine that results likely contributes most to its appetite-stimulating effects as norepinephrine acts at other α-receptors to increase appetite. Mirtazapine also antagonises 5-HT2 receptors, which can

result in appetite stimulation via nuclei within the hypothalamus. It is an off-label drug used for the management of anorexia–cachexia syndrome. [6]

**Dronabinol:** Dronabinol is an orally active cannabinoid that acts on the CNS. Dronabinol is a synthetic form of delta-9-tetrahydro-cannabinol, which is a naturally occurring component of *Cannabis sativa L* and activated cannabinoid receptors (CB) CB1 and CB2. The endogenous cannabinoid system regulates appetite at four functional levels: limbic system, hypothalamus, intestinal, and adipose tissue, using CB1 and CB2 receptors. CB1 is primarily responsible for producing appetite stimulation when activated. Dronabinol directly acts in the vomiting and appetite control centers in the brain, thereby increasing appetite and preventing vomiting. Dronabinol is approved by the U.S. Food and Drug Administration for chemotherapy-related nausea and for AIDS-related anorexia. [7]

**Alcohol:** Alcohol consumption has been suggested to stimulate appetite and potentially increase food intake. Although the mechanisms are unclear, it has been postulated that ingestion of alcohol appears to bypass the satiety mechanisms that modulate short term food intake. Alcohol has been proposed to support an overall increase in food intake in two different pathways one by binding to type-A gamma-aminobutyric acid ($GABA_A$) receptors and stimulating the release of opioid and second by decreasing the serotonin response, a hunger suppresser. Alcoholic beverages may contribute to passive overconsumption of energy from foods. Alcohol may stimulate appetite by increasing desire to eat once eating has begun or by limiting satiety development. Alcohol has been found to have short-term additive effects and changes in appetite regulation, possibly due to its metabolic and psychological effects. Alcoholic beverages suppress fat and carbohydrate oxidation, potentially increasing hunger. This may limit the metabolic satiety signal from fat oxidation. The relatively high energy density of alcoholic beverages may be additive to food energy intake, meaning it may be easier to unintentionally consume excess dietary energy. Alcohol consumption increases acute food intake, and increases total energy intake. [8]

**Cyproheptadine:** Cyproheptadine, an antagonist at the 5-$HT_2$, histamine $H_1$, L-calcium channels and muscarinic cholinergic receptors. It is off label used as an appetite stimulant in malnourished and/or underweight patients with a variety of health conditions, such as cancer, metabolic disease, failure to thrive, malnutrition, HIV, anorexia nervosa and cystic fibrosis. It produces an inhibition of proinsulin synthesis, a reduction in pancreatic insulin and glucose

intolerance. Cyproheptadine affected postprandial satiety or hunger mechanisms, as opposed to food reward or meal-derived satiation. Apart from this cyproheptadine showed increased insulin-like growth factor which is a promoting factor for growth hormone. Another mechanism is related to efficacious role of Cyproheptadine on feeding center in hypothalamus. On the other hand, anticholinergic effect of Cyproheptadine causes reduction in motility of gastrointestinal tract and consequently increasing transit time of food. [9]

**Oxandrolone:** Oxandrolone is an androgen and synthetic anabolic steroid (AAS) medication to help promote weight gain. Oxandrolone is FDA approved for adjunctive therapy to help regain weight they have lost due to certain medical conditions (such as surgery, chronic infection, trauma, long term use of corticosteroid medication such as hydrocortisone/prednisone). Promote weight gain after weight loss due to unknown aetiology. Oxandrolone has been used with dietary protein and energy supplementation to improve body cell mass and muscle strength in patients with chronic malnutrition. Anabolic steroids increase muscle mass through direct and indirect mechanisms. Directly, steroids increase muscle mass by inducing protein synthesis, efficient amino acid utilization, and increasing androgen receptor expression in skeletal muscle. Short-term administration of oxandrolone to healthy young men increased fractional synthesis of muscle protein by 44%. Hypogonadal men treated with Oxandrolone displayed enhanced skeletal muscle mass due to increased mixed muscle protein and myosin heavy chain (MHC) synthesis rates. Oxandrolone act indirectly by antagonism of the glucocorticoid receptor, similar in structure to the androgen receptor, which inhibits protein catabolism. An inductive effect of Oxandrolone on hepatic insulin-like growth factor (IGF)-1 production is also reported to enhance skeletal muscle protein synthesis. [10]

**Glucocorticoids:** Glucocorticoids acts as appetite stimulants by increasing calorie intake. The mechanism of action for appetite stimulation is unknown, but cortisol is thought to have a permissive action for other appetite-stimulating compounds such as opioids and epinephrine, and the ability of corticosteroids to stimulate metabolism has also been suggested to play a role. Glucocorticoids increases appetite by alterations in energy intake, energy expenditure, or substrate oxidation and fat deposition. [11]

**Anamorelin:** Ghrelin is synthesised by the stomach and causes a synergistic rise in growth hormone with additional increase in appetite. The latter causes an increase in oral intake, and so a ghrelin agonist, anamorelin, was produced as an appetite stimulant. This has been trialled in

cancer patients, where it was found to successfully increase oral intake and muscle mass though with an equivocal effect on muscle strength. Ghrelin itself has been shown to increase body mass and muscle mass in a group of cancer patients. Anamorelin showed significant metabolic, clinical, and patient-rated effects in cancer cachexia. [12]

**CONCLUSION:**

Appetite stimulants are essential pharmacological interventions for managing conditions like inadequate food intake and malnutrition. They can increase appetite and maintain nutritional status in patients with poor appetite. These stimulants, including hormonal agents, cannabinoids, and anti-depressants, have unique mechanisms of action. However, their use requires careful consideration of potential side effects and contraindications, as they may not be effective in treating other causes of malnutrition.

**REFERENCES:**

1. Ahima, R. S., & Antwi, D. A. (2008). Brain regulation of appetite and satiety. *Endocrinology and metabolism clinics of North America*, *37*(4), 811–823. https://doi.org/10.1016/j.ecl.2008.08.005
2. Agnew W, Korman R. Pharmacological appetite stimulation. Journal of Feline Medicine and Surgery [Internet]. 2014 Aug 21;16(9):749–756. Available from: https://doi.org/10.1177/1098612x14545273
3. Ebner N, Springer J, Kalantar-Zadeh K, Lainscak M, Doehner W, Anker SD, Von Haehling S. Mechanism and novel therapeutic approaches to wasting in chronic disease. Maturitas [Internet]. 2013 Jul 1;75(3):199–206. Available from: https://doi.org/10.1016/j.maturitas.2013.03.014
4. Adan, R. A., Tiesjema, B., Hillebrand, J. J., la Fleur, S. E., Kas, M. J., & de Krom, M. (2006). The MC4 receptor and control of appetite. *British journal of pharmacology*, *149*(7), 815–827. https://doi.org/10.1038/sj.bjp.0706929
5. Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. Physiology & Behavior [Internet]. 2010 Jul 1;100(5):478–489. Available from: https://doi.org/10.1016/j.physbeh.2010.03.011
6. Hennings, J. M., Heel, S., Lechner, K., Uhr, M., Dose, T., Schaaf, L., Holsboer, F., Lucae, S., Fulda, S., & Kloiber, S. (2019). Effect of mirtazapine on metabolism and

energy substrate partitioning in healthy men. *JCI insight*, *4*(1), e123786. https://doi.org/10.1172/jci.insight.123786

7. Badowski, M. E., & Yanful, P. K. (2018). Dronabinol oral solution in the management of anorexia and weight loss in AIDS and cancer. *Therapeutics and clinical risk management*, *14*, 643–651. https://doi.org/10.2147/TCRM.S126849
8. Yeomans, M. R., Caton, S., & Hetherington, M. M. (2003). Alcohol and food intake. *Current opinion in clinical nutrition and metabolic care*, *6*(6), 639–644. https://doi.org/10.1097/00075197-200311000-00006
9. Najib, K., Moghtaderi, M., Karamizadeh, Z., & Fallahzadeh, E. (2014). Beneficial effect of cyproheptadine on body mass index in undernourished children: a randomized controlled trial. *Iranian journal of pediatrics*, *24*(6), 753–758.
10. Orr R, Singh MF. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders. Drugs [Internet]. 2004 Jan 1;64(7):725–750. Available from: https://doi.org/10.2165/00003495-200464070-00004
11. Reilly JJ, Brougham M, Montgomery C, Richardson F, Kelly A, Gibson BES. Effect of glucocorticoid therapy on energy intake in children treated for acute lymphoblastic leukemia. The Journal of Clinical Endocrinology and Metabolism/Journal of Clinical Endocrinology & Metabolism [Internet]. 2001 Aug 1;86(8):3742–3745. Available from: https://doi.org/10.1210/jcem.86.8.7764
12. Garcia, J. M., Friend, J., & Allen, S. (2013). Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *21*(1), 129–137. https://doi.org/10.1007/s00520-012-1500-1