

APPETITE SUPPRESSANTS

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Introduction and Definition of Appetite Suppressants

Appetite suppressants, scientifically known as **anorectants** or **anorexigenics**, constitute a specific class of pharmacological agents designed primarily to mitigate the sensation of hunger, thereby reducing caloric intake and facilitating weight management. These medications are typically prescribed as adjuncts to comprehensive weight loss programs, especially for individuals suffering from obesity or severe overweight conditions where diet and exercise alone have proven insufficient. The fundamental mechanism involves influencing complex neurochemical pathways within the central nervous system, particularly those regions of the hypothalamus responsible for regulating satiety and feeding behaviors. While the immediate goal is the restriction of appetite, the overarching clinical objective is to achieve and maintain a healthier body weight, consequently reducing the risk factors associated with obesity, such as type 2 diabetes, hypertension, and cardiovascular disease. However, the history of appetite suppressants is fraught with regulatory challenges, significant safety concerns, and ongoing debates regarding their long-term efficacy without concurrent behavioral modifications.

The definition extends beyond simple hunger reduction; effective appetite suppression must translate into a measurable decrease in food consumption patterns over time. These pharmacological interventions target the delicate balance between orexigenic signals (which promote eating) and anorexigenic signals (which inhibit eating). By artificially enhancing the signals of fullness or diminishing the perception of hunger, these drugs aim to reset the patient's internal caloric thermostat to a lower set point. Given the complexity of human eating behavior, which is influenced by psychological, environmental, and physiological factors, these agents are never considered a standalone cure for obesity. Their role is strictly supportive, providing a temporary pharmacological advantage to help patients adhere to necessary dietary restrictions during the initial, challenging phases of weight reduction.

Clinically, the decision to initiate treatment with an anorectant is based on specific criteria, often involving the patient's Body Mass Index (BMI) and the presence of obesity-related comorbidities. For instance, treatment is often considered for individuals with a BMI of 30 or higher, or those with a BMI of 27 or higher who also have significant risk factors such as high cholesterol or sleep apnea. It is crucial to recognize that appetite suppressants are not merely lifestyle drugs but potent medications requiring careful medical supervision due to their potential for serious side effects and, in some historical cases, high potential for dependence or abuse. Therefore, the prescribing physician must conduct a thorough risk-benefit analysis before introduction, monitoring the patient closely throughout the duration of therapy to ensure both safety and therapeutic effectiveness.

Historical Context and Early Stimulant Agents

The earliest successful appetite suppressants were derived from the stimulant class of drugs,

particularly **amphetamines**. Introduced in the mid-20th century, these compounds quickly became popular due to their potent anorectic effects, coupled with mood elevation and increased energy, which were seen as beneficial for adhering to restrictive diets. Amphetamine and its derivatives, such as methamphetamine and dextroamphetamine, primarily exert their effects by increasing the levels of catecholamines--specifically norepinephrine and dopamine--in the brain synapses. This increased presence of neurotransmitters stimulates the satiety center in the hypothalamus, leading to a profound reduction in appetite. The early widespread use of these agents, however, soon revealed significant drawbacks that necessitated a shift in pharmacological development.

The primary concern regarding the use of traditional amphetamines for weight management was their high potential for **addiction and abuse**. Patients often developed tolerance rapidly, requiring increasingly higher doses to achieve the same anorectic effect, leading to physical dependence and psychological compulsion. Furthermore, these potent stimulants carried significant cardiovascular risks, including elevated heart rate, increased blood pressure, and potential for cardiac arrhythmias, making them unsuitable for long-term use in many obese patients who already faced cardiovascular challenges. This unfavorable safety profile led regulatory bodies to severely restrict their use for obesity treatment, prompting researchers to seek structurally related compounds that retained the appetite-suppressing qualities but minimized the psychoactive and addictive properties.

This search led to the development of related, less potent stimulants, most notably **phentermine**. Phentermine acts similarly to amphetamine, increasing catecholamine levels, but its central nervous system stimulating effects are generally less pronounced, offering a better therapeutic index for weight loss management. Phentermine remains one of the most widely prescribed short-term appetite suppressants today. Despite being a controlled substance, it is typically used for periods of up to 12 weeks to initiate weight loss. The historical evolution from highly addictive amphetamines to more specialized agents like phentermine highlights a critical effort in pharmaceutical science to isolate and harness the specific anorectic mechanism while mitigating the severe risks associated with broad, powerful central nervous system stimulation.

Mechanism of Action: Targeting Neurotransmitter Systems

The effectiveness of appetite suppressants hinges upon their ability to modulate key neurotransmitter systems involved in the complex homeostatic and hedonic regulation of food intake. The primary systems targeted include the catecholamine system (dopamine and norepinephrine) and the **serotonergic system** (5-hydroxytryptamine, or 5-HT). Catecholaminergic agents, such as phentermine, act by promoting the release or inhibiting the reuptake of norepinephrine and dopamine in the hypothalamus. The resulting increase in these neurotransmitters in the synaptic cleft activates the neural pathways that convey signals of satiety, effectively overriding the physiological signals of hunger originating from the gut and peripheral

energy stores.

Conversely, serotonergic agents operate by enhancing the activity of serotonin within specific brain regions. Serotonin is known to play a crucial role in mood, sleep, and appetite regulation. Compounds like fenfluramine and dexfenfluramine, now historically significant due to their withdrawal, acted as serotonin agonists or releasers, increasing serotonin levels, which specifically targets the 5-HT_{2C} receptors in the hypothalamus. Activation of these receptors is strongly correlated with the induction of satiety and a reduction in food cravings, particularly for carbohydrates. This distinction is vital: while catecholamine agents often provide a general reduction in hunger, serotonergic agents were sometimes perceived to modulate the hedonic component of eating, making food less rewarding.

Modern pharmacological strategies often involve compounds that target multiple pathways or are used in combination to achieve synergistic effects and enhance efficacy while minimizing dose-related side effects. For instance, some newer FDA-approved treatments combine a stimulant component with a drug that modifies other neurological pathways, such as those regulating seizures or mood, which have incidental weight loss properties. The convergence of these mechanisms--acting on both the basic energy needs (homeostasis) and the pleasure derived from food (hedonics)--underscores the multifaceted challenge of appetite regulation. Understanding the specific neurotransmitter modulation allows clinicians to select treatments based on the patient's individual physiological profile and potential sensitivities to specific classes of drugs.

Major Classes of Appetite Suppressants

Appetite suppressants can be broadly categorized based on their chemical structure and primary mechanism of action, encompassing several distinct pharmacological classes. The first major class comprises the **sympathomimetic amines** (stimulants), which includes phentermine, diethylpropion, and phendimetrazine. These are controlled substances that primarily increase norepinephrine and dopamine activity, leading to central appetite suppression. They are generally approved for short-term use due to the risks of dependence and cardiovascular side effects, and they require strict monitoring of blood pressure and heart rate during treatment. Their rapid action makes them effective for kick-starting weight loss, but their use is limited by duration.

The second, and historically controversial, class includes the **serotonergic agents**, such as fenfluramine and dexfenfluramine. These drugs were highly effective at promoting satiety but were later found to carry unacceptable risks of cardiac valvulopathy (heart-valve defects), leading to their removal from the market globally. The mechanism of heart damage was linked to their agonistic activity at the 5-HT_{2B} receptor, which is expressed in cardiac fibroblasts and mediates the proliferation of valve tissue. This regulatory action marked a critical turning point in the safety assessment of weight loss drugs, prioritizing long-term cardiovascular safety above all else.

A third significant agent was **sibutramine**, which acted as a combined serotonin and norepinephrine reuptake inhibitor (SNRI). Sibutramine offered an appealing dual mechanism, providing both appetite suppression and potentially increased metabolism. However, post-marketing surveillance revealed an increased risk of serious cardiovascular events, including nonfatal myocardial infarction and stroke, particularly in patients with pre-existing cardiovascular disease. Consequently, sibutramine was withdrawn from the market in the United States, Europe, and many other regions in 2010. The withdrawal of both the serotonergic agents and sibutramine cemented the medical community's rigorous skepticism regarding the safety profile of drugs acting broadly on central neurotransmitter systems for chronic weight management.

The Controversy of Phen-Fen and Regulatory Response

The combination therapy known popularly as "**Phen-Fen**" represents one of the most significant pharmacological controversies in the history of weight loss treatment. Phen-Fen involved the simultaneous administration of **phentermine** (a catecholamine-releasing agent) and either **fenfluramine** or its active enantiomer, **dexfenfluramine** (serotonin-releasing agents). The rationale behind this combination was synergistic: phentermine provided immediate appetite control and energy, while the fenfluramine derivatives enhanced satiety, potentially allowing for lower doses of each drug and theoretically reducing individual side effects. This combination achieved substantial popularity and efficacy in the 1990s.

However, widespread clinical use eventually uncovered a devastating and unforeseen side effect: the development of **valvular heart disease**, or cardiac valvulopathy. Studies began to link the use of fenfluramine and dexfenfluramine--and particularly the Phen-Fen combination--to abnormal thickening and dysfunction of the heart valves, most commonly the mitral and aortic valves. This damage impaired the heart's ability to efficiently pump blood and, in severe cases, required surgical intervention. The mechanism, as later determined, was the activation of the 5-HT_{2B} receptor located on heart valve cells, leading to excessive cellular growth and fibrosis.

Faced with compelling epidemiological and clinical evidence documenting these severe, irreversible cardiac defects, the United States Food and Drug Administration (FDA) took decisive action. Fenfluramine and dexfenfluramine were officially requested to be removed from the market in 1997. This withdrawal served as a harsh lesson regarding the long-term, systemic effects of centrally acting weight loss drugs and fundamentally altered the regulatory landscape. The legacy of Phen-Fen emphasized the necessity of extensive, long-term safety studies, especially focusing on cardiovascular outcomes, before any new weight loss medication could gain or maintain market approval. Phentermine, having been judged separately not to carry the same valvulopathy risk, remained available, though often under stricter prescribing guidelines.

Efficacy and Limitations: The Role of Behavioral Management

While appetite suppressants are undeniably effective in reducing caloric intake and facilitating weight loss in the **short term** (typically defined as 6 to 12 months), a critical limitation of these pharmacological interventions is their inability to consistently produce sustained, long-term weight reduction when used in isolation. Clinical trials consistently demonstrate that patients often experience weight regain once the medication is discontinued, a phenomenon often attributed to the body's powerful homeostatic mechanisms fighting to restore the original weight set point, alongside the failure to establish durable lifestyle changes.

Therefore, the empirical evidence overwhelmingly supports the conclusion that appetite suppressants must be used in conjunction with a structured **behavioral management program**. This integrated approach, often referred to as comprehensive obesity management, combines pharmacological support with interventions targeting diet modification, increased physical activity, and cognitive-behavioral strategies aimed at addressing the underlying psychological and habitual factors contributing to weight gain. The medication acts as a crucial tool to ease the initial difficulty of caloric restriction, offering rapid gratification and motivation, but the behavioral component is necessary for teaching the skills required for lifelong weight maintenance.

The necessity of combining pharmacology with behavioral change highlights the distinction between treating a symptom (excessive appetite) and treating the complex disease (obesity). Without addressing deeply ingrained eating habits, emotional triggers for eating, and sedentary behavior, stopping the medication often results in the full return of the factors that drove the initial weight gain. Successful long-term outcomes, defined as maintaining significant weight loss (typically 5% or more of initial body weight) for five years or longer, are overwhelmingly linked to patients who successfully transition from reliance on the drug's effects to mastery of sustainable lifestyle modifications.

Modern Approaches and Current Regulatory Status

Following the withdrawals of sibutramine and the fenfluramine derivatives, the regulatory environment for new appetite suppressants became significantly more stringent. The FDA now requires extensive pre- and post-marketing safety data, particularly concerning cardiovascular safety. This rigorous process has led to the approval of several newer agents and combination drugs that offer improved efficacy profiles and, crucially, better documented long-term safety data than their predecessors. These newer treatments often utilize novel mechanisms or combine existing drugs to target multiple pathways simultaneously.

Modern FDA-approved treatments for chronic weight management include combinations such as phentermine/topiramate extended-release and naltrexone/bupropion extended-release. The phentermine/topiramate combination utilizes the short-term appetite suppression of phentermine

alongside topiramate, an anticonvulsant that has incidental weight loss properties, possibly through appetite suppression and increased satiety. The naltrexone/bupropion combination targets the reward center of the brain; bupropion (an antidepressant) affects dopamine and norepinephrine, and naltrexone (used for opioid/alcohol dependence) blocks opioid receptors, working together to reduce cravings and control eating behavior.

Furthermore, a significant development in the pharmacological treatment of obesity involves injectable agents that are not traditional central nervous system stimulants but rather synthetic analogs of naturally occurring gut hormones, such as Glucagon-like peptide-1 (GLP-1) agonists. While these are technically categorized differently, they exert powerful anorectic effects by slowing gastric emptying and acting on hypothalamic receptors to increase satiety. These agents represent a paradigm shift towards leveraging peripheral hormonal signals rather than relying solely on potent central stimulation, often offering effective weight loss with a different spectrum of side effects, primarily gastrointestinal. These modern agents reflect a comprehensive understanding that effective weight management requires sophisticated, multi-pronged pharmacological intervention tailored for chronic use.

Side Effects and Safety Profile

Despite advancements in formulation and mechanism, all appetite suppressants carry potential side effects, necessitating careful patient selection and continuous monitoring. The sympathomimetic agents (e.g., phentermine) are notorious for their cardiovascular risks.

Cardiovascular Effects: Increased heart rate (tachycardia), elevated blood pressure (hypertension), and palpitations are common. These risks are heightened in patients with pre-existing heart conditions, making these drugs contraindicated in many instances.

Central Nervous System Effects: Insomnia, nervousness, agitation, headache, and dizziness are frequently reported due to the stimulant nature of the drugs. These effects often diminish over time but can necessitate dosage adjustment or discontinuation.

Gastrointestinal Effects: Dry mouth (xerostomia) is highly common with sympathomimetics. Constipation is also a frequently reported side effect.

The side effect profiles of combination drugs and newer agents vary widely. For example, the combination of naltrexone/bupropion often causes nausea, vomiting, and headache, particularly during the initial titration phase, and carries a black box warning regarding suicidal thoughts and behaviors due to the bupropion component. The combination of phentermine/topiramate is associated with neurological issues, including paresthesia (tingling sensations), and carries a risk of metabolic acidosis and acute angle closure glaucoma, requiring ophthalmological monitoring.

The overarching safety concern remains the potential for dependence and abuse, particularly with stimulant-based anorectants. Because of these risks, appetite suppressants are typically

prescribed only when the benefits of weight reduction significantly outweigh the risks associated with the medication. Contraindications are strict, usually excluding patients with severe uncontrolled hypertension, pulmonary hypertension, hyperthyroidism, glaucoma, or a history of drug abuse. Regular follow-up appointments, including checks of blood pressure, heart rate, and psychological status, are mandatory to ensure that the patient is safely benefiting from the pharmacological intervention.

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