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REVIEW

# Smoking, Obesity, and Post-Cessation Weight Gain: Neurobiological Intersection and Treatment Recommendations

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**Abstract:** In the US, 28.8 million adults currently smoke cigarettes, and approximately 1.25 billion people use tobacco globally. Unfortunately, post-cessation weight gain is a substantial barrier to smoking cessation and sustained abstinence. Among people who smoke, 36% meet the body mass index (BMI) criteria for obesity and over 50% meet the waist circumference criteria for central obesity. Despite this, primary care providers currently have limited guidance on how to best treat their patients who want to quit smoking without post-cessation weight gain. There are common neurobiologic and endocrine dysregulations in nicotine dependence and weight gain. For example, nicotine dependence and obesity are both associated with dysregulation in hypothalamic neuropeptide systems and dopaminergic pathways. Medications for nicotine dependence act on dopaminergic pathways and hypothalamic pro-opiomelanocortin (POMC) cells. Similarly, medications for obesity may increase dopamine and norepinephrine signaling and stimulate POMC activity. A unique medication, the fixed-dose extended-release combination of naltrexone and bupropion, supports both smoking cessation and weight loss by increasing dopamine and norepinephrine signaling and stimulating POMC-producing cells. This narrative review outlines neurobiologic mechanisms common to smoking and obesity and compares the effects of available pharmacotherapies on dopaminergic system and neuroendocrine dysregulation. Finally, this review outlines factors that primary care professionals should consider when treating people who want to stop smoking but are at risk of post-cessation weight gain.

**Keywords:** brain mechanisms, pharmacotherapy, primary care, smoking cessation, weight gain

## Introduction

Approximately 1.25 billion people 15 years and older globally use tobacco, and 28.8 million adults in the US currently smoke cigarettes.[1,2] Among people who smoke in the US, 68% express a desire to stop smoking.[1] Unfortunately, 77% to 86% of people who stop smoking gain weight in the first year of abstinence.[3] In the US, 36% of people who smoke also have obesity,[4] and obesity affects over 890 million adults globally.[5] For individuals with obesity, additional weight gain may present a substantial health risk and a barrier to smoking cessation. Thus, primary care professionals who are helping their patients quit smoking must often address the potential for post-cessation weight gain.

Studies have shown an association between chronic smoking and lower body weight.[6–8] Conversely, smoking cessation is associated with weight gain and higher body weight.[3,9–11] According to a 2012 meta-analysis, mean post-cessation weight gain 1 year after quitting smoking is 4.67 kg (10.3 lb), and 13% to 14% of people who quit smoking gain more than 10 kg (22 lb).[3] People with higher baseline body weights tend to have greater post-cessation weight gain than those with lower baseline body weights,[12] and post-cessation weight gain may result in patients meeting the criteria for obesity (body mass index [BMI] ≥30) or a higher class of obesity.

Post-cessation weight gain is a significant health concern, regardless of a patient's BMI, as it is associated with an increase in hypertension[13] and type 2 diabetes.[14] Compared with BMI, central obesity is more predictive of cardiovascular disease and all-cause mortality.[15,16] People who currently and formerly smoked were more likely to have central

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obesity (≥85 cm for women and ≥90 cm for men) than those who never smoked, according to an analysis of the Korea National Health and Nutrition Examination Survey.[17] Central obesity is generally defined as a waist circumference ≥105 cm for women and ≥110 cm for men (with lower thresholds for people with Asian ancestry) or waist-to-hip ratio of ≥0.85 for women and ≥0.95 for men.[15,16] Among people who smoke, 54% had a waist circumference in the central obesity category (defined as >35 inches or 89 cm for women and >40 inches or 102 cm for men) according to an analysis of the US National Health and Nutrition Examination Survey (NHANES).[4,17] The health risks associated with central obesity, which are exacerbated by smoking, highlight the importance of addressing post-cessation weight gain with patients who want to stop smoking to prevent additional health consequences.

The long-term benefits of smoking cessation substantially outweigh the health risks associated with post-cessation weight gain;[18] however, patients who express concerns about post-cessation weight gain have lower rates of smoking abstinence.[19] Moreover, weight gain is associated with relapse back to smoking.[20–22] Women report that they are willing to gain a mean of 2.3 kg (5 lb) after smoking cessation, while men report that they are willing to gain a mean of 4.9 kg (10 lb), with a rising risk of smoking relapse above these thresholds.[23] A recent meta-analysis found that managing weight gain during smoking cessation significantly improved smoking abstinence rates.[24] Unfortunately, the medications currently available for smoking cessation have relatively small effects on post-cessation weight gain (<1 kg at 1 year).[25–27] A medication that could aid in smoking cessation and attenuate or eliminate post-cessation weight gain would have undeniable benefits for people who want to stop smoking.

In this review, we provide an overview of evidence-based treatments for patients who want to quit smoking and reduce or eliminate post-cessation weight gain. We outline key underlying brain mechanisms implicated in nicotine dependence and weight gain, including effects on hypothalamic systems and dopaminergic pathways. We then explore the role of available medications that might be used by primary care providers for smoking cessation, obesity, and post-cessation weight gain.

## Neurobiology of Weight Regulation, Obesity, and Nicotine Dependence

Activity in the hypothalamus and mesolimbic "reward" pathway is central to nicotine dependence as well as central hunger, satiety, and the motivation to eat.[28–36] Obesity is now recognized as being primarily a neuroendocrine disease[37] that results in impaired systems of hunger and satiety[38] as well as metabolic disruption.[39] While hypothalamic systems are generally associated with homeostatic eating (food consumption in response to metabolic signals), the mesolimbic reward system is typically associated with non-homeostatic, "hedonic" eating (food consumption for its rewarding properties, regardless of metabolic status or the food's nutritional value).[40] More specifically, the hypothalamus integrates peripheral input regarding the body's energy balance and then responds to this input through a variety of neuropeptides and connections with mesolimbic pathways.[41–43] In the mesolimbic pathway, activation of neurons in the ventral tegmental area (VTA) results in dopamine release into the nucleus accumbens (NAc), prefrontal cortex, and other brain structures, ultimately giving rise to appetitive and reward-motivated behaviors, such as eating and smoking (Figure 1A).[44] Addictive substances, like nicotine, "hijack" neurobiologic systems that can regulate reward pathways and appetitive processes governing food intake.[45–47]

### Neurobiology of Weight Regulation

Energy balance and weight regulation are controlled in part by communication between the hypothalamic neuroendocrine system and the mesolimbic reward pathway. In the hypothalamus, first-order neurons in the arcuate nucleus receive information about the body's energy balance by detecting serum levels of insulin, leptin, and glucagon-like peptide 1 (GLP-1).[50,51] One subpopulation of these arcuate nucleus neurons produces the orexigenic (hunger-inducing) neuropeptide, agouti-related peptide (AgRP), while another subpopulation produces the anorexigenic (satiety-inducing) neuropeptide, pro-opiomelanocortin (POMC). These POMC and AgRP neurons project to other areas of the hypothalamus and the brainstem to control and coordinate hunger and satiety responses as well as energy expenditure and other metabolic processes.[41,52–54] Despite the fact that appetitive pathways are classified as "hedonic" and satiety pathways are classified as "homeostatic", the 2 systems are in constant communication.[55] One component of this interactive neuroendocrine system is activation of the mesolimbic system.[56,57] Neurons in the VTA express dopamine and receptors for hypothalamic neuropeptides involved in

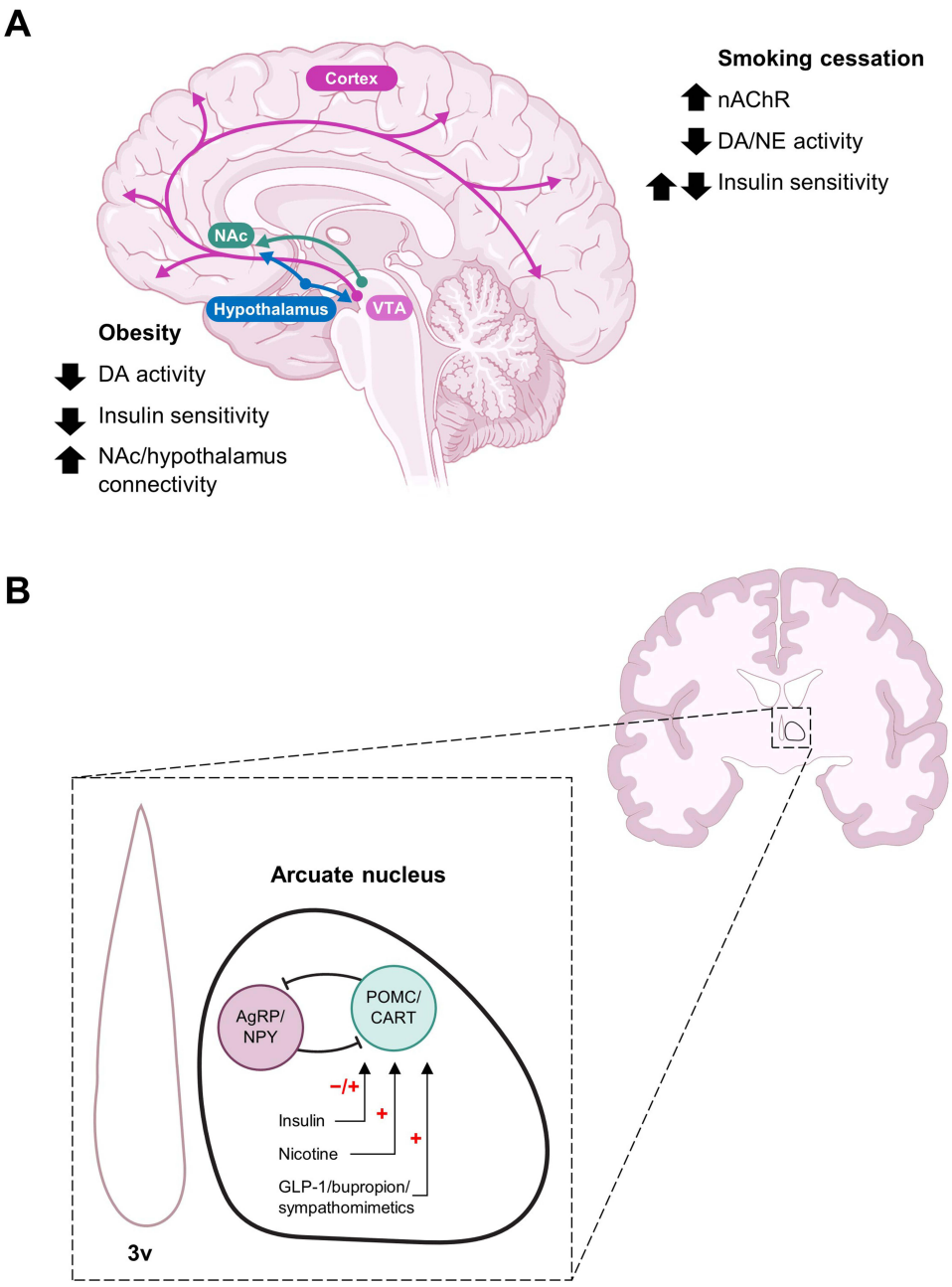


**Figure 1** Neurobiology of obesity and smoking addiction. (**A**) The hypothalamus interacts with the mesolimbic pathway via connections with the VTA and NAc. Smoking addiction upregulates the nAChR, can bidirectionally impact insulin sensitivity, and downregulates dopamine and norepinephrine signaling. Obesity also downregulates dopamine signaling, reduces insulin sensitivity, and increases connectivity between the NAc and hypothalamus. Adapted from Xu H, Yang F. The interplay of dopamine metabolism abnormalities and mitochondrial defects in the pathogenesis of schizophrenia. Transl Psychiatry. 2022;12(1):464. (http://creativecommons.org/licenses/by/4.0/).[48] (**B**) In the arcuate nucleus of the hypothalamus (shown in a coronal brain slice), POMC- and AgRP-producing neurons reciprocally inhibit one another and can be stimulated or inhibited by insulin signaling and stimulated by nicotine, GLP-1, bupropion, and sympathomimetics to promote satiety. In obesity, insulin preferentially inhibits POMC activity. Adapted from Baik JH. Dopaminergic control of the feeding circuit. Endocrinol Metab (Seoul). 2021;36(2):229–239. (https://creativecommons.org/licenses/by-nc/4.0/).[49]
**Abbreviations**: AgRP, agouti-related peptide; CART, cocaine and amphetamine regulated transcript; DA, dopamine; GLP-1, glucagon-like peptide 1; NAc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NE, norepinephrine; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; VTA, ventral tegmental area; 3V, third ventricle.

hunger and satiety, such as the POMC product melanocortin.[58] These neuropeptides activate the VTA, which in turn releases dopamine into the NAc and can promote eating.[56,57] Taken together, the hypothalamic neuroendocrine system activates and regulates the mesolimbic reward pathway in the brain to regulate food intake.


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## Neuroendocrine Dysregulation in Obesity

As a neuroendocrine disorder, obesity is associated primarily with dysregulation of the neuroendocrine system, with some involvement of the mesolimbic brain pathways.[37–39] The volume of the hypothalamus, including the energy-sensing arcuate nucleus, is greater in people with a BMI ≥25 than in those with a BMI <25.[59] Moreover, higher BMI and central obesity (measured by waist circumference) are associated with greater disruptions in hypothalamic cellular structures.[60,61] These structural disruptions may be caused by inflammation, given that hypothalamic inflammation is associated with higher BMI, greater central obesity, greater visceral fat, and metabolic disease.[62] Additionally, people with obesity (BMI >25) compared to people with a BMI <25 have greater functional connectivity between the hypothalamus and the NAc.[55] This increased connectivity between homeostatic (hypothalamus) and mesolimbic (NAc) regions may contribute to hypothalamic and mesolimbic dysregulation.

Individuals with obesity also show lower activation of circuits involved in the response to food consumption, with decreased dopamine binding in the ventral striatum.[63] Some studies have associated obesity with reduced dopamine receptor availability in the striatum.[30,31] In contrast, a recent meta-analysis found that differences in dopamine receptor availability between individuals with obesity and those without obesity were only consistent among those with a BMI ≥40.[64,65] On the other hand, a 2019 meta-analysis found that stimulating dopamine receptors led to decreases in body weight, BMI, and waist circumference in patients with prolactinomas who were treated with dopamine agonists.[66] Thus, the available evidence suggests a link between a dysregulated dopaminergic system and obesity in some people, which may drive overconsumption of highly palatable foods and be improved by restoring dopamine transmission.

## Neurobiology of Nicotine Dependence

In the brain, nicotine binds and activates nicotinic acetylcholine receptors (nAChRs), receptors that are normally activated by acetylcholine.[67,68] There is a high density of nAChRs in brain structures associated with motivation, including the VTA, NAc, prefrontal cortex, and hypothalamus.[69,70] When nicotine binds to nAChRs, it triggers dopamine release from the VTA to the NAc,[67,68] enhancing reward and motivation. Additionally, nicotine increases POMC neuron activity in the hypothalamus to promote satiety.[32] Thus, nicotine affects both hypothalamic and mesolimbic systems.

Chronic nicotine use leads to dysregulation of both hypothalamic and mesolimbic systems and precipitates symptoms of nicotine withdrawal during smoking abstinence. Studies have found that smoking leads to an upregulation of nAChRs throughout the brain, with people who smoke expressing 27% greater levels of nAChRs in the striatum compared with people who do not smoke.[28,29] The degree of nAChR upregulation is associated with the severity of withdrawal symptoms and difficulty quitting smoking.[71] With extensive nAChR upregulation, acetylcholine signaling is insufficient to bind the larger population of nAChRs, and the resulting understimulation results in nicotine withdrawal symptoms during smoking abstinence.[72] While smoking upregulates nAChRs, it downregulates dopamine receptors, leading to decreased reward from acetylcholine and nicotine and the experience of nicotine tolerance.[73–75]

The severity of nicotine withdrawal symptoms is highly predictive of smoking relapse.[74] Clinically, nicotine withdrawal commonly includes irritability, insomnia, anxiety, difficulty concentrating, agitation, fatigue, depressed mood, restlessness, hunger, and weight gain.[76] Nicotine withdrawal is associated with decreased signaling of dopamine,[77,78] norepinephrine, serotonin, and other neurotransmitters in mesolimbic brain structures. In contrast to the stimulation of reward systems seen in acute nicotine use (eg, in a nicotine-naïve patient), chronic nicotine use is associated with decreased mesolimbic reward processing[79] and dysregulation of mesolimbic reward systems.[67,68] Pharmacotherapies that treat nicotine withdrawal (nicotine replacement, bupropion) lead to increased signaling of dopamine, norepinephrine, and other neurotransmitters.[72,80–82]

## The Neurobiological Intersection of Nicotine Dependence and Obesity

Both nicotine dependence and weight regulation occur through neuroendocrine and mesolimbic pathways. A pathway found in both is the hypothalamic neuropeptide system.[32,43] Specifically, nicotine activates the POMC system, which has been known to promote satiety;[32] however, insulin can inhibit POMC activity in people with obesity and promote hunger (Figure 1B).[39] Similarly, increased levels of AgRP have been associated with food cravings,[83] and AgRP-producing

neuron activity can promote insulin resistance.[84] Nicotine can either enhance or reduce insulin sensitivity,[85] resulting in bidirectional effects on body weight.[86] For example, chronic nicotine use can either promote insulin sensitivity and decreased body weight or promote insulin resistance and increased body weight. Importantly, insulin resistance is associated with greater visceral fat accumulation, which may contribute to increased central obesity among some people who smoke.[4,17,86] Similarly, smoking more heavily (more cigarettes per day) is associated with increased rates of obesity and higher weight gain after smoking cessation.[87] Thus, while nicotine may promote satiety and lower body weight in some people via increased POMC activity, smoking may also lead to insulin resistance and increased central adiposity in other people, possibly via dysregulation of POMC neurons and insulin resistance. In addition to the association of smoking with dysregulation of metabolic processes, smoking cessation is commonly associated with weight gain due to the removal of the excitatory effects of nicotine on hypothalamic and metabolic systems.[88]

The dopaminergic system is also implicated in weight gain and nicotine dependence.[30,31,64,73,75] During nicotine withdrawal, people experience a hypodopaminergic state[78] that is quite similar to the hypodopaminergic state found in people with hedonic eating.[89] It is now hypothesized that reduced dopamine transmission may be a cause of food cravings.[90] Although there is conflicting evidence regarding the effects of smoking and smoking cessation on metabolic rate,[91,92] many people engage in increased hedonic eating during nicotine withdrawal,[93,94] possibly due to a hypodopaminergic state. In summary, smoking cessation and obesity are each independently associated with dysregulation of the dopaminergic system.[64,65] As such, people with obesity who also smoke commonly experience significant weight gain when trying to stop smoking.[3]

# Treatments

## Evidence-Based Treatments for Smoking Cessation

Pharmacotherapies for smoking cessation target the nAChR or increase neurotransmitters (eg, dopamine and norepinephrine) that are low during nicotine withdrawal. Varenicline binds the nAChR at the nicotine binding site, blocking nicotine from binding to the nAChR and preventing nicotine-mediated reward.[95,96] Bupropion inhibits the reuptake of norepinephrine and dopamine in the neuronal synapse to increase mesolimbic activity, which is reduced during withdrawal.[81,82,97,98] Nicotine replacement therapies (eg, nicotine patch, gum, lozenge, inhaler, and nasal spray) increase dopamine transmission by binding to and activating nAChRs in the mesolimbic system to restore diminished dopamine transmission during withdrawal.[99,100] According to a 2013 meta-analysis, odds ratios for biochemically verified 6-month post-quit smoking abstinence rates compared with placebo were 2.88 for varenicline, 1.82 for bupropion, and 1.84 for nicotine replacement therapies.[101] Another option available for smoking cessation in the United Kingdom, Canada, and some European countries, cytisine, has a similar mechanism of action to varenicline (ie, nAChR blockade).[102] Cytisine was associated with biochemically verified smoking abstinence in 32.6% of patients compared with just 7% for patients receiving placebo at 12 weeks in a randomized controlled trial.[103]

## Evidence-Based Treatments for Obesity

FDA-approved antiobesity medications work through several mechanisms. Nutrient-stimulated hormone–based pharmacotherapies (including the GLP-1 receptor [GLP-1R] agonists liraglutide, semaglutide, and tirzepatide) increase satiety via central effects.[104–106] While GLP-1R agonists do not readily cross the blood-brain barrier, some peripherally administered GLP-1R agonists like semaglutide may access certain brain regions.[107–109] In the brain, GLP-1R agonists can engage hypothalamic systems by preferentially targeting the GLP-1R in the hypothalamus, especially on POMC-producing neurons in the arcuate nucleus, promoting satiety.[107,110] These injectable medications lead to substantial weight loss, ranging from an 11% to 23% reduction in body weight in 56 to 72 weeks.[104,111–114] Sympathomimetics (including diethylpropion, phendimetrazine, benzphetamine, and phentermine + topiramate extended release [ER]) are amphetamine derivatives that increase the release of norepinephrine and, to a lesser extent, dopamine in the hypothalamus to stimulate POMC activity,[115–120] suppress appetite, and reduce body weight by 5% to 10% within 24 weeks.[116–120] Sympathomimetic medications have been associated with side effects such as increased blood pressure and insomnia.[116,121] Fixed-dose ER combination of naltrexone and bupropion (NB-ER) is a reward system regulator medication designed to treat obesity. The bupropion component of NB-ER increases the activity of

norepinephrine and dopamine in the hypothalamus, which stimulates POMC cells.[115,122,123] NB-ER may also prevent the subsequent inhibition of POMC cells by the inhibitory opioid neuropeptide beta-endorphin[122,123] as well as alter mesolimbic dopamine activity via the naltrexone component.[124,125] NB-ER use results in an average of 5% to 12% weight loss in 56 weeks.[122,123,126,127] To our knowledge, NB-ER is the only medication currently available that targets both the hypothalamic and mesolimbic systems involved in weight regulation.

## Potential Treatments for Post-Cessation Weight Gain

Currently, the FDA has not approved a medication for the management of post-cessation weight gain. Compared with placebo, varenicline was associated with very modest attenuation of post-cessation weight gain over 12 weeks, but effects were no longer significant after 1 year.[25] Similarly, the nicotine patch significantly attenuated post-cessation weight gain, but the effects only persisted while patients were using the patch.[26,128] Bupropion has demonstrated the most promising attenuation of post-cessation weight gain, but effects were still modest (1.1 kg) at end of treatment.[27] While cytisine is used in some countries for smoking cessation, its effects on post-cessation weight gain have not been assessed.[103] A systematic review by the Cochrane Collaboration found mean attenuation of post-cessation weight gain for smoking cessation medications at end of treatment was −1.01 kg for bupropion, −0.52 kg for nicotine replacement therapy, and −0.23 kg for varenicline.[129] Although bupropion showed the largest attenuation of post-cessation weight gain, no medication thus far eliminates post-cessation weight gain.

Based on the known mechanisms of weight gain through hypothalamic and mesolimbic systems, several treatments are now being explored for smoking cessation and prevention of post-cessation weight gain. Despite the robust effects of nutrient-stimulated hormone–based medications on weight loss, recent studies have found that a GLP-1R agonist did not improve smoking cessation outcomes above those of placebo or varenicline alone.[130,131]

Interestingly, NB-ER, which is approved by the FDA for the treatment of obesity, has also been shown to reduce nicotine withdrawal symptoms and food cravings.[132] As a reward system regulator, NB-ER can help to prevent weight gain 6 months after smoking cessation in individuals with obesity.[132] Treatment with NB-ER reduced waist circumference by a mean of 7 cm, as opposed to a reduction of 3 cm with the GLP-1R agonist liraglutide.[133] Thus, among emerging treatments, NB-ER appears to be the most promising to help people quit smoking without gaining weight. Consistent with these findings, the Association for the Study of Obesity on the Island of Ireland recommends NB-ER as the first choice of treatment for patients with obesity who smoke.[134]

# Clinical Recommendations

Providers should consider treatments to attenuate or prevent post-cessation weight gain for patients who want to quit smoking and (1) have obesity or a BMI >27 with an obesity-associated complication; (2) have a history of significant post-cessation weight gain; or (3) are at risk of not quitting or relapse back to smoking due to weight gain.[135,136]

## Recommendations for Co-Occurring Obesity and Smoking Cessation

Currently, obesity treatment guidelines recommend pharmacologic treatment as part of a multifactorial approach to obesity management, along with medical nutrition, physical activity, and, in some cases, metabolic (or bariatric) surgery.[137–141] The American Association of Clinical Endocrinologists recommends the use of antiobesity medications in people with progressive weight gain, and the American Association of Clinical Endocrinologists, the Endocrine Society, and Obesity Canada all recommend antiobesity medication for patients with a BMI ≥27 with obesity-related complications, such as type 2 diabetes, cardiovascular disease, or metabolic syndrome.[137] Although specific US guidance on choosing a pharmacotherapy to treat co-occurring obesity and smoking cessation is limited, the Association for the Study of Obesity on the Island of Ireland recommends the use of NB-ER in patients who smoke and have obesity.[134]

Guidelines for treating each condition highlight multifactorial approaches to treatment. In addition to pharmacotherapy for both conditions, lifestyle modifications, such as increased physical activity and medical nutrition for obesity and behavioral counseling and mindfulness for smoking cessation, should be considered.[129,138,139,142,143] Primary care professionals should discuss the treatment options with patients, considering their individual goals for weight management, their prior experiences with post-cessation weight gain, and their expectations regarding treatment route and side

effects. Moreover, clinicians should consider simultaneously continuing or starting antiobesity medications with smoking cessation medications to mitigate the negative impacts of both conditions on patient health.

### Recommendations for Post-Cessation Weight Gain

As weight gain is a major barrier to smoking cessation and a driver of relapse,[21,22] there is a clear need for pharmacotherapies to manage post-cessation weight gain. Unfortunately, guidance on treating post-cessation weight gain is limited. Currently, the most effective FDA-approved pharmacotherapy for smoking cessation among those concerned about weight gain is bupropion,[129] though treatment effects are modest.[27] The most promising emergent treatment for smoking cessation and prevention of post-cessation weight gain appears to be NB-ER.[132] Primary care professionals should discuss the treatment options for smoking cessation with patients, considering the impact of each medication on post-cessation weight gain and the concerns patients have regarding weight gain. For patients with concerns about weight gain, primary care professionals should consider treatment options, regardless of BMI, to improve the likelihood of successful smoking cessation and prolonged abstinence.

## Conclusions

Weight gain after smoking cessation presents a substantial barrier to stopping smoking and to sustained smoking abstinence around the world. Weight gain after smoking cessation is critically important for people with BMI-based or central obesity, who may develop comorbidities with additional weight gain. Similarly, post-cessation weight gain is also important when treating people without obesity who may relapse back to smoking after significant post-cessation weight gain. The drivers of smoking and obesity share neurobiologic mechanisms in neuroendocrine and mesolimbic systems, suggesting the potential of pharmacologic treatments that target these shared mechanisms. Although existing smoking cessation pharmacotherapies have only modest effects on post-cessation weight gain, international guidelines highlight that existing obesity treatments, such as NB-ER, may have promise as treatments for post-cessation weight gain.

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## References

1. VanFrank B, Malarcher A, Cornelius ME, Schecter A, Jamal A, Tynan M. Adult smoking cessation: United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2024;73(29):633–641. doi:10.15585/mmwr.mm7329a1

2. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000-2030. 2024. Available from: https://www.who.int/publications/i/item/9789240088283. Accessed March 31, 2025.
3. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. *Br Med J*. 2012;345:e4439. doi:10.1136/bmj.e4439
4. Ellison-Barnes A, Yeh HC, Pollack CE, et al. Weighing cessation: rising adiposity of current smokers in NHANES. *Prev Med*. 2023;175:107713. doi:10.1016/j.ypmed.2023.107713
5. World Health Organization. Obesity and overweight. Updated March 1, 2024, Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed June 21, 2024.
6. Patel M, Kaufman A, Hunt Y, Nebeling L. Understanding the relationship of cigarette smoking trajectories through adolescence and weight status in young adulthood in the United States. *J Adolesc Health*. 2017;61(2):163–170. doi:10.1016/j.jadohealth.2017.02.005
7. Munafo MR, Tilling K, Ben-Shlomo Y. Smoking status and body mass index: a longitudinal study. *Nicotine Tob Res*. 2009;11(6):765–771. doi:10.1093/ntr/ntp062
8. Plurphanswat N, Rodu B. The association of smoking and demographic characteristics on body mass index and obesity among adults in the U.S. 1999-2012. *BMC Obes*. 2014;1:18. doi:10.1186/s40608-014-0018-0
9. Williamson DF, Madans J, Anda RF, Kleinman JC, Giovino GA, Byers T. Smoking cessation and severity of weight gain in a national cohort. *N Engl J Med*. 1991;324(11):739–745. doi:10.1056/NEJM199103143241106
10. Kruger J, Ham SA, Prohaska TR. Behavioral risk factors associated with overweight and obesity among older adults: the 2005 National Health Interview Survey. *Prev Chronic Dis*. 2009;6(1):A14.
11. Tian J, Venn A, Otahal P, Gall S. The association between quitting smoking and weight gain: a systemic review and meta-analysis of prospective cohort studies. *Obes Rev*. 2016;17(10):1014. doi:10.1111/obr.12448
12. Krotter A, Garcia-Perez A, Aonso-Diego G, Garcia-Fernandez G. Body weight change during a smoking cessation intervention for individuals with overweight or obesity. *Eat Behav*. 2024;53:101882. doi:10.1016/j.eatbeh.2024.101882
13. Ninomiya Y, Kawasoe S, Kubozono T, et al. Association between weight gain following smoking cessation and development of hypertension in the future. *Hypertens Res*. 2024;47(5):1167–1174. doi:10.1038/s41440-023-01549-8
14. Wu L, Wang X, Dong JY, Zhao YT, Lou H. Smoking cessation, weight gain, and risk for type 2 diabetes: a prospective study. *Int J Public Health*. 2022;67:1604654. doi:10.3389/ijph.2022.1604654
15. Bosomworth NJ. Normal-weight central obesity: unique hazard of the toxic waist. *Can Fam Physician*. 2019;65(6):399–408. doi:10.1787/health_glance-2017-en
16. Franek E, Pais P, Basile J, et al. General versus central adiposity as risk factors for cardiovascular-related outcomes in a high-risk population with type 2 diabetes: a post hoc analysis of the REWIND trial. *Cardiovasc Diabetol*. 2023;22(1):52. doi:10.1186/s12933-023-01757-z
17. Kim Y, Jeong SM, Yoo B, Oh B, Kang HC. Associations of smoking with overall obesity, and central obesity: a cross-sectional study from the Korea national health and nutrition examination survey (2010-2013). *Epidemiol Health*. 2016;38:e2016020. doi:10.4178/epih.e2016020
18. Suutari-Jaasko A, Ylitalo A, Ronkaine J, Huikuri H, Kesaniemi YA, Ukkola OH. Smoking cessation and obesity-related morbidities and mortality in a 20-year follow-up study. *PLoS One*. 2022;17(12):e0279443. doi:10.1371/journal.pone.0279443
19. Tuovinen EL, Saarni SE, Kinnunen TH, et al. Weight concerns as a predictor of smoking cessation according to nicotine dependence: a population-based study. *Nordisk Alkohol Nark*. 2018;35(5):344–356. doi:10.1177/1455072518800217
20. Kuo CW, Lin CF, Chen CY, et al. Body-weight gain in women during smoking cessation is a sex-specific predictor of 6-month abstinence: a retrospective cohort study. *Front Public Health*. 2022;10:872220. doi:10.3389/fpubh.2022.872220
21. Norregaard J, Tonnesen P, Petersen L. Predictors and reasons for relapse in smoking cessation with nicotine and placebo patches. *Prev Med*. 1993;22(2):261–271. doi:10.1006/pmed.1993.1021
22. Borrelli B, Spring B, Niaura R, Hitsman B, Papandonatos G. Influences of gender and weight gain on short-term relapse to smoking in a cessation trial. *J Consult Clin Psychol*. 2001;69(3):511–515. doi:10.1037//0022-006x.69.3.511
23. Pomerleau CS, Kurth CL. Willingness of female smokers to tolerate postcessation weight gain. *J Subst Abuse*. 1996;8(3):371–378. doi:10.1016/s0899-3289(96)90215-1
24. Garcia-Fernandez G, Krotter A, Gonzalez-Roz A, Garcia-Perez A, Secades-Villa R. Effectiveness of including weight management in smoking cessation treatments: a meta-analysis of behavioral interventions. *Addict Behav*. 2023;140:107606. doi:10.1016/j.addbeh.2023.107606
25. Sun Y, Duan W, Meng X, Li H, Jia C. Varenicline is associated with a modest limitation in weight gain in smokers after smoking cessation: a meta-analysis. *J Public Health (Oxf)*. 2018;40(2):e126–e132. doi:10.1093/pubmed/fdx056
26. Dale LC, Schroeder DR, Wolter TD, Croghan IT, Hurt RD, Offord KP. Weight change after smoking cessation using variable doses of transdermal nicotine replacement. *J Gen Intern Med*. 1998;13(1):9–15. doi:10.1046/j.1525-1497.1998.00002.x
27. Yang M, Chen H, Johnson ML, et al. Comparative effectiveness of smoking cessation medications to attenuate weight gain following cessation. *Subst Use Misuse*. 2016;51(5):586–597. doi:10.3109/10826084.2015.1126744
28. Breese CR, Marks MJ, Logel J, et al. Effect of smoking history on [3H]nicotine binding in human postmortem brain. *J Pharmacol Exp Ther*. 1997;282(1):7–13. doi:10.1016/S0022-3565(24)36798-9
29. Staley JK, Krishnan-Sarin S, Cosgrove KP, et al. Human tobacco smokers in early abstinence have higher levels of beta2* nicotinic acetylcholine receptors than nonsmokers. *J Neurosci*. 2006;26(34):8707–8714. doi:10.1523/JNEUROSCI.0546-06.2006
30. de Weijer BA, van de Giessen E, van Amelsvoort TA, et al. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. *EJNMMI Res*. 2011;1(1):37. doi:10.1186/2191-219X-1-37
31. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet*. 2001;357(9253):354–357. doi:10.1016/s0140-6736(00)03643-6
32. Mineur YS, Abizaid A, Rao Y, et al. Nicotine decreases food intake through activation of POMC neurons. *Science*. 2011;332(6035):1330–1332. doi:10.1126/science.1201889
33. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab*. 2008;7(5):400–409. doi:10.1016/j.cmet.2008.03.007
34. Kallo I, Omrani A, Meye FJ, de Jong H, Liposits Z, Adan RAH. Characterization of orexin input to dopamine neurons of the ventral tegmental area projecting to the medial prefrontal cortex and shell of nucleus accumbens. *Brain Struct Funct*. 2022;227(3):1083–1098. doi:10.1007/s00429-021-02449-8

35. Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. *Science*. 2007;317(5843):1355. doi:10.1126/science.1144599
36. Omrani A, de Vrind VAJ, Lodder B, et al. Identification of novel neurocircuitry through which leptin targets multiple inputs to the dopamine system to reduce food reward seeking. *Biol Psychiatry*. 2021;90(12):843–852. doi:10.1016/j.biopsych.2021.02.017
37. Ferreira-Hermosillo A, de Miguel Ibanez R, Perez-Dionisio EK, Villalobos-Mata KA. Obesity as a neuroendocrine disorder. *Arch Med Res*. 2023;54(8):102896. doi:10.1016/j.arcmed.2023.102896
38. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875–E891. doi:10.1503/cmaj.191707
39. Dodd GT, Michael NJ, Lee-Young RS, et al. Insulin regulates POMC neuronal plasticity to control glucose metabolism. *Elife*. 2018;7:e38704. doi:10.7554/eLife.38704
40. Campos A, Port JD, Acosta A. Integrative hedonic and homeostatic food intake regulation by the central nervous system: insights from neuroimaging. *Brain Sci*. 2022;12(4):431. doi:10.3390/brainsci12040431
41. Jais A, Bruning JC. Arcuate nucleus-dependent regulation of metabolism-pathways to obesity and diabetes mellitus. *Endocr Rev*. 2022;43(2):314–328. doi:10.1210/endrev/bnab025
42. Jin R, Sun S, Hu Y, Zhang H, Sun X. Neuropeptides modulate feeding via the dopamine reward pathway. *Neurochem Res*. 2023;48(9):2622–2643. doi:10.1007/s11064-023-03954-4
43. Mangieri LR, Lu Y, Xu Y, et al. A neural basis for antagonistic control of feeding and compulsive behaviors. *Nat Commun*. 2018;9(1):52. doi:10.1038/s41467-017-02534-9
44. Yohn SE, Galbraith J, Calipari ES, Conn PJ. Shared behavioral and neurocircuitry disruptions in drug addiction, obesity, and binge eating disorder: focus on group I mGluRs in the mesolimbic dopamine pathway. *ACS Chem Neurosci*. 2019;10(5):2125–2143. doi:10.1021/acschemneuro.8b00601
45. Alhadeff AL, Goldstein N, Park O, Klima ML, Vargas A, Betley JN. Natural and drug rewards engage distinct pathways that converge on coordinated hypothalamic and reward circuits. *Neuron*. 2019;103(5):891–908e6. doi:10.1016/j.neuron.2019.05.050
46. Koob GF, Le Moal M. Addiction and the brain antireward system. *Annu Rev Psychol*. 2008;59:29–53. doi:10.1146/annurev.psych.59.103006.093548
47. Tan B, Browne CJ, Nobauer T, Vaziri A, Friedman JM, Nestler EJ. Drugs of abuse hijack a mesolimbic pathway that processes homeostatic need. *Science*. 2024;384(6693). doi:10.1126/science.adk6742
48. Xu H, Yang F. The interplay of dopamine metabolism abnormalities and mitochondrial defects in the pathogenesis of schizophrenia. *Transl Psychiatry*. 2022;12(1):464. doi:10.1038/s41398-022-02233-0
49. Baik JH. Dopaminergic control of the feeding circuit. *Endocrinol Metab (Seoul)*. 2021;36(2):229–239. doi:10.3803/EnM.2021.979
50. Roh E, Choi KM. Hormonal gut-brain signaling for the treatment of obesity. *Int J Mol Sci*. 2023;24(4):3384. doi:10.3390/ijms24043384
51. Souza GF, Solon C, Nascimento LF, et al. Defective regulation of POMC precedes hypothalamic inflammation in diet-induced obesity. *Sci Rep*. 2016;6(1):29290. doi:10.1038/srep29290
52. De Solis AJ, Del Rio-Martin A, Radermacher J, et al. Reciprocal activity of AgRP and POMC neurons governs coordinated control of feeding and metabolism. *Nat Metab*. 2024;6(3):473–493. doi:10.1038/s42255-024-00987-z
53. Garfield AS, Li C, Madara JC, et al. A neural basis for melanocortin-4 receptor-regulated appetite. *Nat Neurosci*. 2015;18(6):863–871. doi:10.1038/nn.4011
54. Wang D, He X, Zhao Z, et al. Whole-brain mapping of the direct inputs and axonal projections of POMC and AgRP neurons. *Front Neuroanat*. 2015;9:40. doi:10.3389/fnana.2015.00040
55. Contreras-Rodriguez O, Vilar-Lopez R, Andrews ZB, Navas JF, Soriano-Mas C, Verdejo-Garcia A. Altered cross-talk between the hypothalamus and non-homeostatic regions linked to obesity and difficulty to lose weight. *Sci Rep*. 2017;7(1):9951. doi:10.1038/s41598-017-09874-y
56. Norgren R, Hajnal A, Mungarndee SS. Gustatory reward and the nucleus accumbens. *Physiol Behav*. 2006;89(4):531–535. doi:10.1016/j.physbeh.2006.05.024
57. Dunigan AI, Roseberry AG. Actions of feeding-related peptides on the mesolimbic dopamine system in regulation of natural and drug rewards. *Addict Neurosci*. 2022;2:100011. doi:10.1016/j.addicn.2022.100011
58. Dunigan AI, Olson DP, Roseberry AG. VTA MC3R neurons control feeding in an activity- and sex-dependent manner in mice. *Neuropharmacology*. 2021;197:108746. doi:10.1016/j.neuropharm.2021.108746
59. Brown SSG, Westwater ML, Seidlitz J, Ziauddeen H, Fletcher PC. Hypothalamic volume is associated with body mass index. *Neuroimage Clin*. 2023;39:103478. doi:10.1016/j.nicl.2023.103478
60. Thomas K, Beyer F, Lewe G, et al. Higher body mass index is linked to altered hypothalamic microstructure. *Sci Rep*. 2019;9(1):17373. doi:10.1038/s41598-019-53578-4
61. Venkatasubramanian PN, Keni P, Gastfield R, et al. Diffusion tensor imaging detects acute and subacute changes in corpus callosum in blast-induced traumatic brain injury. *ASN Neuro*. 2020;12(1):1759091420922929. doi:10.1177/1759091420922929
62. Kullmann S, Abbas Z, Machann J, et al. Investigating obesity-associated brain inflammation using quantitative water content mapping. *J Neuroendocrinol*. 2020;32(12):e12907. doi:10.1111/jne.12907
63. Guo J, Simmons WK, Herscovitch P, Martin A, Hall KD. Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. *Mol Psychiatry*. 2014;19(10):1078–1084. doi:10.1038/mp.2014.102
64. Ribeiro G, Maia A, Cotovio G, Oliveira FPM, Costa DC, Oliveira-Maia AJ. Striatal dopamine D2-like receptors availability in obesity and its modulation by bariatric surgery: a systematic review and meta-analysis. *Sci Rep*. 2023;13(1):4959. doi:10.1038/s41598-023-31250-2
65. Weir CB, Jan A. *BMI Classification Percentile and Cut off Points*. StatPearls. StatPearls Publishing; 2024.
66. Byberg S, Futtrup J, Andreassen M, Krogh J. Metabolic effects of dopamine agonists in patients with prolactinomas: a systematic review and meta-analysis. *Endocr Connect*. 2019;8(10):1395–1404. doi:10.1530/EC-19-0286
67. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*. 1996;382(6588):255–257. doi:10.1038/382255a0
68. Brody AL, Mandelkern MA, Olmstead RE, et al. Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. *Neuropsychopharmacology*. 2009;34(2):282–289. doi:10.1038/npp.2008.87

69. Zhang D, Gao M, Xu D, et al. Impact of prefrontal cortex in nicotine-induced excitation of ventral tegmental area dopamine neurons in anesthetized rats. *J Neurosci*. 2012;32(36):12366–12375. doi:10.1523/JNEUROSCI.5411-11.2012
70. Calarco CA, Li Z, Taylor SR, et al. Molecular and cellular characterization of nicotinic acetylcholine receptor subtypes in the arcuate nucleus of the mouse hypothalamus. *Eur J Neurosci*. 2018;48(1):1600–1619. doi:10.1111/ejn.13966
71. Brody AL, Mukhin AG, Mamoun MS, et al. Brain nicotinic acetylcholine receptor availability and response to smoking cessation treatment: a randomized trial. *JAMA Psychiatry*. 2014;71(7):797–805. doi:10.1001/jamapsychiatry.2014.138
72. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57–71. doi:10.1146/annurev.pharmtox.48.113006.094742
73. Fehr C, Yakushev I, Hohmann N, et al. Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *Am J Psychiatry*. 2008;165(4):507–514. doi:10.1176/appi.ajp.2007.07020352
74. Robinson JD, Li L, Chen M, et al. Evaluating the temporal relationships between withdrawal symptoms and smoking relapse. *Psychol Addict Behav*. 2019;33(2):105–116. doi:10.1037/adb0000434
75. Yasuno F, Ota M, Ando K, et al. Role of ventral striatal dopamine D1 receptor in cigarette craving. *Biol Psychiatry*. 2007;61(11):1252–1259. doi:10.1016/j.biopsych.2006.06.028
76. Wills L, Kenny PJ. Addiction-related neuroadaptations following chronic nicotine exposure. *J Neurochem*. 2021;157(5):1652–1673. doi:10.1111/jnc.15356
77. Jackson KJ, Muldoon PP, De Biasi M, Damaj MI. New mechanisms and perspectives in nicotine withdrawal. *Neuropharmacology*. 2015;96(Pt B):223–234. doi:10.1016/j.neuropharm.2014.11.009
78. Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. *Biol Psychiatry*. 2012;71(3):184–191. doi:10.1016/j.biopsych.2011.07.024
79. Oliver JA, Evans DE, Addicott MA, Potts GF, Brandon TH, Drobes DJ. Nicotine withdrawal induces neural deficits in reward processing. *Nicotine Tob Res*. 2017;19(6):686–693. doi:10.1093/ntr/ntx067
80. McCaul ME, Wand GS, Kuwabara H, Dannals RF, Wong D, Xu X. The relationship of varenicline agonism of alpha4beta2 nicotinic acetylcholine receptors and nicotine-induced dopamine release in nicotine-dependent humans. *Nicotine Tob Res*. 2020;22(6):892–899. doi:10.1093/ntr/ntz080
81. Piacentini MF, Clinckers R, Meeusen R, Sarre S, Ebinger G, Michotte Y. Effect of bupropion on hippocampal neurotransmitters and on peripheral hormonal concentrations in the rat. *J Appl Physiol*. 2003;95(2):652–656. doi:10.1152/japplphysiol.01058.2002
82. Bruijnzeel AW. Tobacco addiction and the dysregulation of brain stress systems. *Neurosci Biobehav Rev*. 2012;36(5):1418–1441. doi:10.1016/j.neubiorev.2012.02.015
83. Haseltine KN, Robins H, Cohen V, et al. MON-321 AgRP and food cravings decrease with treatment of Cushing's disease. *J Endocr Soc*. 2020;4(Suppl 1):MON–321. doi:10.1210/jendso/bvaa046.1401
84. Steculorum SM, Ruud J, Karakasilioti I, et al. AgRP neurons control systemic insulin sensitivity via myostatin expression in brown adipose tissue. *Cell*. 2016;165(1):125–138. doi:10.1016/j.cell.2016.02.044
85. Wu Y, Song P, Zhang W, et al. Activation of AMPKalpha2 in adipocytes is essential for nicotine-induced insulin resistance in vivo. *Nat Med*. 2015;21(4):373–382. doi:10.1038/nm.3826
86. Kullmann S, Valenta V, Wagner R, et al. Brain insulin sensitivity is linked to adiposity and body fat distribution. *Nat Commun*. 2020;11(1):1841. doi:10.1038/s41467-020-15686-y
87. Dare S, Mackay DF, Pell JP. Relationship between smoking and obesity: a cross-sectional study of 499,504 middle-aged adults in the UK general population. *PLoS One*. 2015;10(4):e0123579. doi:10.1371/journal.pone.0123579
88. Driva S, Korkontzelou A, Tonstad S, Tentolouris N, Katsaounou P. The effect of smoking cessation on body weight and other metabolic parameters with focus on people with type 2 diabetes mellitus. *Int J Environ Res Public Health*. 2022;19(20):13222. doi:10.3390/ijerph192013222
89. Majuri J, Joutsa J, Johansson J, et al. Dopamine and opioid neurotransmission in behavioral addictions: a comparative PET study in pathological gambling and binge eating. *Neuropsychopharmacology*. 2017;42(5):1169–1177. doi:10.1038/npp.2016.265
90. Palavra NC, Lubomski M, Flood VM, Davis RL, Sue CM. Increased added sugar consumption is common in Parkinson's disease. *Front Nutr*. 2021;8:628845. doi:10.3389/fnut.2021.628845
91. Bradley DP, Johnson LA, Zhang Z, et al. Effect of smoking status on total energy expenditure. *Nutr Metab (Lond)*. 2010;7(1):81. doi:10.1186/1743-7075-7-81
92. Hofstetter A, Schutz Y, Jequier E, Wahren J. Increased 24-hour energy expenditure in cigarette smokers. *N Engl J Med*. 1986;314(2):79–82. doi:10.1056/NEJM198601093140204
93. Anker JJ, Nakajima M, Raatz S, Allen S, al'Absi M. Tobacco withdrawal increases junk food intake: the role of the endogenous opioid system. *Drug Alcohol Depend*. 2021;225:108819. doi:10.1016/j.drugalcdep.2021.108819
94. Rodin J. Weight change following smoking cessation: the role of food intake and exercise. *Addict Behav*. 1987;12(4):303–317. doi:10.1016/0306-4603(87)90045-1
95. Chantix (varenicline). *Package insert. Pfizer*; 2011.
96. Tonstad S, Arons C, Rollema H, et al. Varenicline: mode of action, efficacy, safety and accumulated experience salient for clinical populations. *Curr Med Res Opin*. 2020;36(5):713–730. doi:10.1080/03007995.2020.1729708
97. Zyban (bupropion HCl). *Package Insert*. GSK; 2021.
98. Warner C, Shoaib M. How does bupropion work as a smoking cessation aid? *Addict Biol*. 2005;10(3):219–231. doi:10.1080/13556210500222670
99. Nicotrol NS (nicotine nasal spray). *Package Insert*. Pfizer; 2010.
100. Molyneux A. Nicotine replacement therapy. *BMJ*. 2004;328(7437):454–456. doi:10.1136/bmj.328.7437.454
101. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;2013(5):CD009329. doi:10.1002/14651858.CD009329.pub2
102. World Health Organization. The global health observatory: cytisine. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-tobacco-offerhelp-medication-cytisine-place-available. Accessed March 12, 2025.

103. Rigotti NA, Benowitz NL, Prochaska J, et al. Cytisinicline for smoking cessation: a randomized clinical trial. *JAMA*. 2023;330(2):152–160. doi:10.1001/jama.2023.10042
104. Tronieri JS, Wadden TA, Walsh O, et al. Effects of liraglutide on appetite, food preoccupation, and food liking: results of a randomized controlled trial. *Int J Obes (Lond)*. 2020;44(2):353–361. doi:10.1038/s41366-019-0348-6
105. Victoza (liraglutide). *Package Insert*. Novo Nordisk; 2017.
106. Zepbound (tirzepatide). *Package Insert*. Eli Lilly; 2023.
107. Gabery S, Salinas CG, Paulsen SJ, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight*. 2020;5(6): e133429. doi:10.1172/jci.insight.133429
108. Huang KP, Acosta AA, Ghidewon MY, et al. Dissociable hindbrain GLP1R circuits for satiety and aversion. *Nature*. 2024;632(8025):585–593. doi:10.1038/s41586-024-07685-6
109. Rhea EM, Babin A, Thomas P, et al. Brain uptake pharmacokinetics of albiglutide, dulaglutide, tirzepatide, and DA5-CH in the search for new treatments of Alzheimer's and Parkinson's diseases. *Tissue Barriers*. 2024;12(4):2292461. doi:10.1080/21688370.2023.2292461
110. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124(10):4473–4488. doi:10.1172/JCI75276
111. Trenson L, Trenson S, van Nes F, et al. Liraglutide for weight management in the real world: significant weight loss even if the maximal daily dose is not achieved. *Obes Facts*. 2022;15(1):83–89. doi:10.1159/000520217
112. Pi-Sunyer X. SCALE obesity and prediabetes investigators. Liraglutide in weight management. *N Engl J Med*. 2015;373(18):1781–1782. doi:10.1056/NEJMc1509759
113. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA*. 2022;327(2):138–150. doi:10.1001/jama.2021.23619
114. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205–216. doi:10.1056/NEJMoa2206038
115. Stăcescu Ș, Hancu G, Podar D, Todea Ș, Tero-Vescan A. A historical overview upon the use of amphetamine derivatives in the treatment of obesity. *J Pharm Care*. 2019;7:72–79. doi:10.18502/jpc.v7i3.2355
116. Cercato C, Roizenblatt VA, Leanca CC, et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. *Int J Obes (Lond)*. 2009;33(8):857–865. doi:10.1038/ijo.2009.124
117. Guo F, Garvey WT. Cardiometabolic disease staging predicts effectiveness of weight-loss therapy to prevent type 2 diabetes: pooled results from Phase III clinical trials assessing phentermine/topiramate extended release. *Diabetes Care*. 2017;40(7):856–862. doi:10.2337/dc17-0088
118. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, Phase 3 extension study. *Am J Clin Nutr*. 2012;95(2):297–308. doi:10.3945/ajcn.111.024927
119. Nuako A, Tu L, Reyes KJC, Chhabria SM, Stanford FC. Pharmacologic treatment of obesity in reproductive aged women. *Curr Obstet Gynecol Rep*. 2023;12(2):138–146. doi:10.1007/s13669-023-00350-1
120. Lomaira (phentermine hydrocloride USP). *Package Insert*. KVK-Tech, Inc; 2016.
121. Qsymia (Phentermine and Topiramate Extended-Release). *Package Insert*. Vivus, LLC; 2023.
122. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)*. 2009;17(1):30–39. doi:10.1038/oby.2008.461
123. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013;21(5):935–943. doi:10.1002/oby.20309
124. Roberto da Silva G, Carneiro MG, Barbosa MP, et al. Naltrexone/bupropion modifies weight, food intake, and Drd2 gene expression in rats. *J Endocrinol*. 2022;253(3):85–96. doi:10.1530/JOE-21-0393
125. Levy A, Daniels S, Hudson R, et al. Bupropion and naltrexone combination alters high fructose corn syrup self-administration and gene expression in rats. *Neuropharmacology*. 2018;135:547–554. doi:10.1016/j.neuropharm.2018.01.035
126. Onakpoya IJ, Lee JJ, Mahtani KR, Aronson JK, Heneghan CJ. Naltrexone-bupropion (Mysimba) in management of obesity: a systematic review and meta-analysis of unpublished clinical study reports. *Br J Clin Pharmacol*. 2020;86(4):646–667. doi:10.1111/bcp.14210
127. Fujioka K, Plodkowski R, O'Neil PM, Gilder K, Walsh B, Greenway FL. The relationship between early weight loss and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy. *Int J Obes (Lond)*. 2016;40(9):1369–1375. doi:10.1038/ijo.2016.67
128. Jorenby DE, Hatsukami DK, Smith SS, et al. Characterization of tobacco withdrawal symptoms: transdermal nicotine reduces hunger and weight gain. *Psychopharmacology (Berl)*. 1996;128(2):130–138. doi:10.1007/s002130050118
129. Hartmann-Boyce J, Theodoulou A, Farley A, et al. Interventions for preventing weight gain after smoking cessation. *Cochrane Database Syst Rev*. 2021;10(10):CD006219. doi:10.1002/14651858.CD006219.pub4
130. Lengsfeld S, Burkard T, Meienberg A, et al. Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial. *EClinicalMedicine*. 2023;57:101865. doi:10.1016/j.eclinm.2023.101865
131. Luthi H, Lengsfeld S, Burkard T, et al. Effect of dulaglutide in promoting abstinence during smoking cessation: 12-month follow-up of a single-centre, randomised, double-blind, placebo-controlled, parallel group trial. *EClinicalMedicine*. 2024;68:102429. doi:10.1016/j.eclinm.2024.102429
132. Wilcox CS, Oskooilar N, Erickson JS, et al. An open-label study of naltrexone and bupropion combination therapy for smoking cessation in overweight and obese subjects. *Addict Behav*. 2010;35(3):229–234. doi:10.1016/j.addbeh.2009.10.017
133. Welling MS, de Groot CJ, Mohseni M, et al. Treatment with liraglutide or naltrexone-bupropion in patients with genetic obesity: a real-world study. *EClinicalMedicine*. 2024;74:102709. doi:10.1016/j.eclinm.2024.102709
134. Le Roux CW, Fitzgerald I, Neff K. ASOI adult obesity clinical practice guideline adaptation. Available from: https://asoi.info/guidelines/pharmacotherapy/. Accessed July 25, 2024.
135. Pankova A, Kralikova E, Zvolska K, et al. Early weight gain after stopping smoking: a predictor of overall large weight gain? A single-site retrospective cohort study. *BMJ Open*. 2018;8(12):e023987. doi:10.1136/bmjopen-2018-023987
136. Scherr A, Seifert B, Kuster M, et al. Predictors of marked weight gain in a population of health care and industrial workers following smoking cessation. *BMC Public Health*. 2015;15:520. doi:10.1186/s12889-015-1854-7

137. Garvey WT, Mechanick JI, Brett EM, et al. American association of clinical endocrinologists and American college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(Suppl 3):1–203. doi:10.4158/EP161365.GL
138. Pederson SD, Manjoo P, Wharton S. Canadian adult obesity clinical practice guidelines: pharmacotherapy for obesity management. Available from: https://obesitycanada.ca/guidelines/pharmacotherapy. Accessed June 26, 2024.
139. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity guideline resources. The Endocrine Society. Available from: https://www.endocrine.org/clinical-practice-guidelines/pharmacological-management-of-obesity. Accessed June 26, 2024.
140. Glazer S, Biertho L. Canadian adult obesity clinical practice guidelines: bariatric surgery: selection & pre-operative workup. Available from: https://obesitycanada.ca/guidelines/preop. Accessed May 10, 2024.
141. Brown J, Clarke C, Johnson Stoklossa C, Sievenpiper C. Canadian adult obesity clinical practice guidelines: medical nutrition therapy in obesity management. Obesity Canada Updated October 21, 2022, Available from: https://obesitycanada.ca/guidelines/nutrition. Accessed May 10, 2024.
142. Davis JM, Goldberg SB, Anderson MC, Manley AR, Smith SS, Baker TB. Randomized trial on mindfulness training for smokers targeted to a disadvantaged population. *Subst Use Misuse*. 2014;49(5):571–585. doi:10.3109/10826084.2013.770025
143. US Preventive Services Task Force, Krist AH, Davidson KW, et al. Interventions for tobacco smoking cessation in adults, including pregnant persons: US preventive services task force recommendation statement. *JAMA*. 2021;325(3):265–279. doi:10.1001/jama.2020.25019