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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

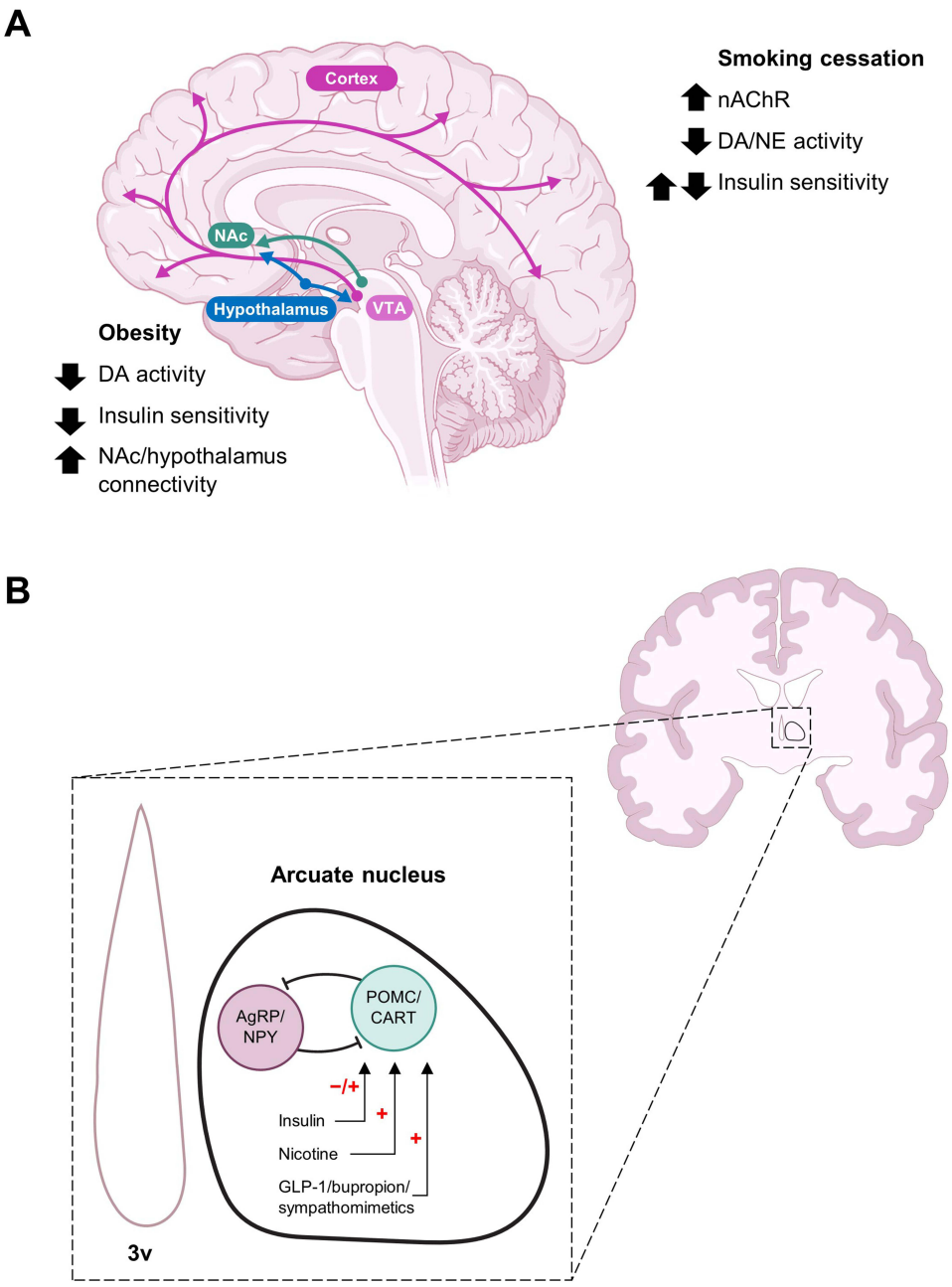

Figure 1 Neurobiology of obesity and smoking addiction. (**A**) The hypothalamus interacts with the mesolimbic pathway via connections with the VTA and NAc. Smoking addiction upregulates the nAChR, can bidirectionally impact insulin sensitivity, and downregulates dopamine and norepinephrine signaling. 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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