Pharmacologic Intervention in Habitual Smoking

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The health risks associated with smoking justify efforts at cessation. Of the 50 million smokers in the United States, about 20 million attempt to quit each year. Approximately 6% are successful. Nicotine, the addictive agent within tobacco smoke, acts to enhance the release of neurotransmitters in the pleasure reinforcing area of the brain. Nicotine replacement therapy has been successfully used to relieve patients' withdrawal symptoms when cessation has been attempted. Nicotine replacement is available as a gum, patch, inhaler, and nasal spray. Bupropion, an antidepressant, is the first non-nicotine drug approved for smoking cessation. It blocks the neuronal uptake of serotonin and norepinephrine. Bupropion, like nicotine replacement therapy, is twice as effective as a placebo in smoking cessation.

Introduction

The health risks due to smoking warrant significant efforts at successful smoking cessation in as many people as possible. Of the 50 million smokers in the United States, about 20 million attempt to quit each year. Approximately 6% succeed in quitting long term (1). Behavior modification is the most important aspect in the process of smoking cessation, but when used as the sole means of treatment it is often insufficient. Drug therapy, used as an adjunct to behavioral addictive-disorder and relapse prevention, has become an important aid in cessation therapy.

The most common pharmacologic smoking cessation aid is nicotine replacement therapy (NRT). Two of the four forms of nicotine delivery are now available over the counter and recently bupropion, an antidepressant, was approved for use in smoking cessation. This article discusses how these products work and covers patient education necessary to maximize successful smoking cessation.

Nicotine Pharmacodynamics, or What the Drug Does to the Body

Nicotine is a ganglionic (nicotinic) cholinergic-receptor agonist that acts on receptors in the brain (autonomic ganglia, adrenal medulla, and neuromuscular junctions) and other organs. Growth hormone, prolactin, vasopressin, adrenocorticotropic hormone, and cortisol are all released by nicotine (2). Acting presynaptically, nicotine enhances the release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, serotonin, beta-endorphin, and others. Activating neurons in the mesolimbic system, nicotine enhances dopamine release in the nucleus accumbens, the pleasure-reinforcing area of the brain affected by addictive drugs such as cocaine, heroine, and amphetamines (3). Some pharmacological effects of nicotine are listed in Table 1. These responses give the smoker both positive and negative reinforcement.

Pharmacokinetics of Nicotine, or What the Body Does to the Drug

Nicotine is a weak base (2). Absorption through the buccal mucosa, respiratory tract, and skin depends on the pH of the delivery system. With cigarettes, the delivery system is smoke, which is acidic; therefore buccal absorption of nicotine is poor, but nicotine is readily absorbed from the lungs due to the large surface area and extensive blood supply. Nicotine enters the blood stream from the lungs and is rapidly distributed to the heart and brain. After 10-19 seconds in the brain, nicotine concentrations fall due to uptake by peripheral tissues. The elimination half-life of nicotine is two to three hours, and concentrations accumulate over six to eight hours during regular smoking or nicotine dosing (5). Primarily eliminated by hepatic metabolism, nicotine has an extensive first pass effect and is, hence, not active in an oral form (6).

Table 1. Some effects of nicotine.

- Relaxation during stress
- Improved attention, learning, reaction time and problem solving
- Reduced hunger
- Relief of anxiety
- Increased metabolism
- Decreased body weight
- Heart rate acceleration
- Cutaneous and coronary vasoconstriction
- Increased blood pressure
- Increased cardiac output
- Peripheral vasoconstriction
- Increased low density lipoproteins, very low density lipoproteins, and decreased high density lipoproteins

Dependence

Dependence, or addiction, is a disease process characterized by the continued use of a specific psychoactive substance despite physical, psychological, and/or social harm. The World Health Organization describes drug dependence as "a behavioral pattern in which the use of a given psychoactive drug is given a sharply higher priority over other behaviors which once had significantly higher value." Withdrawal symptoms can begin a few hours after smoking cessation, peak in one to four days, and begin to diminish by two to four weeks. Desire to smoke can persist for months or years after cessation. Drug treatment with NRT is used to establish and to sustain nicotine levels for a time period necessary to avoid relapse. Problems occurring during cessation include depression and increased hunger resulting in weight gain (5).

It was once believed that nicotine was responsible for changes in drug metabolism. The changes are actually caused by a group of chemicals in cigarette smoke know as polycyclic aromatic hydrocarbons that cause changes in the cytochrome P450 enzymes, specifically the CYP1A2 isoenzyme. Theophylline, tacrine, acetaminophen, caffeine, and clozapine are all drugs metabolized by CYP1A2, and smokers may require higher doses of these and other medications metabolized by CYP1A2 to achieve a therapeutic response (5).

Other drug interactions involve the hemodynamic effects of nicotine in cigarette smoke. Changes in response, such as decreased anti-hypertensive responses; increased risks of myocardial infarction, stroke, and thromboembolic disease in women on estrogen products; decreased sedative effects of diazepam; and decreased response to H_2-receptor antagonists are all possible with cigarette smoking. Patients attempting smoking cessation should have dosages of such medications, especially theophylline, adjusted (5).

Nicotine Replacement Therapy

NRT can relieve patients' withdrawal symptoms when smoking cessation is attempted, without exposing the patient to the toxins of cigarette smoke, while removing the sensory pleasures associated with varying levels of nicotine. There are four available delivery methods for NRT: gum, patch, nasal spray, and inhaler (6). NRT helps smokers quit by three mechanisms:

- Reducing withdrawal symptoms, which can promote relapse
- Partially satisfying cravings
- Preserving effects such as desirable mood, attention states, and handling stressful or boring situations

Nicotine Gum

Nicotine gum is designed to release nicotine when chewed, allowing the drug to be absorbed through the buccal mucosa. Food and drink affect the absorption of the nicotine, and patients must be counseled to avoid food or drink for 15 minutes before using the gum. This product is available over the counter in 2 mg and 4 mg products. The 4 mg product is best for people who smoke more than 20-25 cigarettes per day (3). Product information recommends six weeks of dosing followed by six weeks of dose tapering though recent studies suggest longer periods of therapy may be required (7).

Patients should be instructed to chew one or two pieces per hour, as recent data show scheduled dosing to be more effective than ad lib dosing. Patients should chew the gum slowly until they feel a mild tingling sensation, then park the gum between the cheek and gum till the sensation ends. This process should be repeated for around 30 minutes per piece of gum (3). Patients generally absorb 0.8 to 0.9 mg of nicotine from a 2-mg piece of gum. Ten to twelve doses per day will provide 10 mg or 20 mg of nicotine from the 2 mg and 4 mg pieces, respectively. This supplies one-third to one-half the usual intake of nicotine from a 30 cigarette a day habit (6).

Nicotine Patches

Nicotine patches are easy to use and are available over the counter in a variety of strengths. Most current

recommendations for dosing schedules appear to under-treat smokers. Standard 21-22 mg patches have been shown to deliver around 54% of the levels achieved when smoking. Patients who smoke >40 cigarettes per day should be started on doses of 42-44 mg/day (3). Patches are available in 24 hour and 16 hour release rates. Sixteen-hour patches may relieve nicotine-induced insomnia while reducing desensitization and tolerance to nicotine. Patients who experience early morning withdrawal should use the 24-hour patch, which may also improve compliance as it is replaced at the same time each day. Combining the use of the patch with nicotine gum can significantly reduce withdrawal symptoms compared with the use of either product alone, as demonstrated by Fagerström in a 1993 study (6).

Nicotine Nasal Spray

Nicotine nasal spray achieves twice the smoking cessation rates as placebo but requires more patient counseling than the patch, as it is more complicated to use. It is especially effective for the heavy smoker but does require a prescription (6). The most common side effect is nasal irritation that generally diminishes with time (3).

Patients using nicotine spray should be advised to:

- Spray against the lower nasal mucosa.
- Avoid sniffing or spraying the upper nasal passages.
- Start at one to two doses per hour, not to exceed five doses per hour or 40 doses per day (15 doses per day is average, one spray in each nostril equals one dose).
- Expect to use one to two canisters per week at the start of therapy.
- Continue therapy for an average of 12 weeks, but some patients may need to continue therapy beyond this time frame (3). Use of the spray for over three months has not been shown to increase efficacy.

Nicotine Inhaler

The nicotine inhaler, the newest NRT product available, is shaped like a cigarette and is especially helpful for patients needing the ritual of smoking (7). It also requires a prescription. It is actually not an inhaler as the drug is absorbed buccally and does not reach the lungs. Vaporized nicotine from a capsule within the puffer is delivered to the mucosa of the mouth and the posterior pharynx. Eighty puffs over 20 minutes will deliver approximately 2 mg of nicotine, the maximum deliverable amount per capsule. Initial dosing is 6-16 capsules per day (3).

Bupropion

Bupropion, marketed as Zyban® or Wellbutrin SR®, is the first non-nicotine drug approved for use in smoking cessation (6). Bupropion is an antidepressant that has both noradrenergic and dopaminergic activity. It is a weak blocker of the neuronal uptake of serotonin and norepinephrine and also inhibits the neuronal re-uptake of dopamine to some extent (8). Nicotine stimulates the release of dopamine, norepinephrine, and other neurotransmitters, which become important in the development of nicotine dependence. Norepinephrine in the locus caeruleus activates the alertness, increased concentration, and memory associated with smoking. Dopamine stimulates the nucleus accumbens, the pleasure reinforcing area of the brain. Lack of norepinephrine and dopamine stimulation when nicotine is discontinued may account for nicotine withdrawal symptoms (3).

There are three active metabolites of bupropion: hydroxybupropion (comparable in potency to bupropion), threohydrobupropion, and erythrohydrobupropion (both 1/10 to 1/2 as potent as bupropion). Steady state plasma concentrations of bupropion and metabolites are reached within five to eight days. Drugs that interact with bupropion include orphenadrine, cyclophosphamide, and MAO inhibitors. Carbamazepine, phenobarbital, and phenytoin induce metabolism of bupropion, and cimetidine inhibits metabolism (8). Ritonavir can also increase serum bupropion concentration (6). The half-life of bupropion is significantly prolonged in alcohol liver disease.

Bupropion treatment should be continued for no longer than 12 weeks dosed at 150 mg daily for three days, then increased to 150 mg twice daily. Patients should choose a quit date after steady state has been achieved, usually day eight of therapy. Doses of greater than 300 mg per day have been associated with seizure activity and should be avoided. The goal of therapy is complete abstinence and, if this is not achieved by week seven, it is unlikely that the cessation attempt will be successful. In this case therapy should therefore be discontinued after this time and attempted again later (6).

The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown but, like NRT, it is twice as effective as placebo in smoking cessation. One study showed that bupropion use with NRT produced even higher rates of cessation than bupropion alone or NRT alone (7). Bupropion also appears to slow down the weight gain associated with smoking cessation (3). Jorenby et al compared placebo with nicotine patches, with bupropion, and with bupropion plus nicotine patches. By week seven of therapy subjects in the placebo group had gained an average of 2.1 kg. The NRT patch group had gained an average of 1.6 kg, the bupropion group an average of 1.7 kg, and the combination

group gained an average of 1.1 kg (9). The most common side effects reported by patients in smoking cessation trials included dry mouth and insomnia (3).

Other Drugs Used for Cessation

Clonidine, effective in opiate and alcohol withdrawal, has been studied for smoking cessation, but success has been limited to women and patients with a history of depression. Other studies have shown it to be effective only in the first four weeks of therapy, with no significant benefit over placebo after the first four weeks (6).

Anxiolytic agents have been used in an attempt to reduce the anxiety associated with nicotine withdrawal (6). Diazepam was found to reduce the anxiety, but had no effect on abstinence. Hydroxyzine, meprobamate, and buspirone have been shown to be ineffective. Tricyclic antidepressants imipramine and doxepin have not been proven effective in cessation. Mecamylamine, a nicotinic receptor antagonist, has however shown some promise especially when used with NRT. Lobeline, a weak nicotinic agonist, was removed from the over-the-counter market in 1993 because there was no evidence to demonstrate efficacy though a homeopathic product that contains very small amounts of lobeline is still on the market. Homeopathic products are not evaluated by the FDA for safety or efficacy (6).

Conclusion

Today there is help for patients who desire to stop smoking. Both NRT and bupropion have been proven to double the success rate of cessation. Patients should be educated about the health benefits of smoking cessation as well as the available products, both over the counter and prescription. Physicians and health care workers should encourage all patients who smoke to begin the process of quitting.

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