REVIEW

TRUDY D. HELGE, PsyD
Postdoctoral Fellow in Clinical/Health Psychology, Co-Director, Cleveland Clinic Smoking Cessation Program, Department of Psychiatry and Psychology, Cleveland Clinic

GARLAND Y. DENELSKY, PhD
Director, Cleveland Clinic Smoking Cessation Program, Department of Psychiatry and Psychology, Cleveland Clinic

Pharmacologic aids to smoking cessation

ABSTRACT

Nicotine replacement and bupropion have shown significant benefits for those seeking pharmacologic assistance with smoking cessation. This discussion reviews the efficacy literature for both treatments, including potential side effects.

KEY POINTS

Pharmacologic aids can help some smokers to quit, but are no panacea, yielding substantially lower success rates than behaviorally oriented programs that use a variety of techniques.

Drug interventions roughly double short-term quit rates when used with other minimal interventions.

Of the pharmacologic aids other than nicotine replacement, only the antidepressant bupropion has been consistently demonstrated to assist smokers to quit. It may be used in combination with nicotine replacement. As with nicotine replacement, bupropion's long-term success rates are modest.

Appropriate psychological interventions can substantially enhance pharmacologic techniques.

DRUG INTERVENTIONS CAN HELP the smoker to quit, an increasing number of studies show, but are clearly no panacea and should not be presented to the smoker as such. Pharmacologic interventions, along with minimal additional intervention, have been shown to roughly double the short-term quit rates. Furthermore, although long-term quit rates using pharmacologic methods alone are quite modest, rarely exceeding 20% at 1 year, multicomponent behaviorally oriented programs have yielded biochemically validated long-term quit rates in the range of 30% to 40%.[1]

A physician may choose to use pharmacologic interventions as a first-line effort at cessation, which, if unsuccessful, should be followed by referral to a behaviorally oriented multicomponent smoking cessation program.

Above all, the physician should repeatedly urge each smoker to quit, since physician advice has been demonstrated as the most effective means of motivating smokers to attempt to quit smoking.[2]

NICOTINE REPLACEMENT THERAPY

The idea for nicotine replacement therapy was derived from nicotine's well-known addictive quality. Rather than impose noxious, negative reinforcement (as was attempted, albeit unsuccessfully, with nicotine antagonists) nicotine replacement techniques minimize or eliminate physiological withdrawal symptoms. The ex-smoker is then, ideally, better able to weaken and ultimately break the conditioned associations between smoking and situations, persons, or emotional states.[3]

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Nicotine chewing gum

Initially available only by prescription, nicotine chewing gum was made available over-the-counter in the United States in 1984. It is available in 2-mg and 4-mg strengths. Users are instructed to chew the gum slowly, whenever cravings arise. The nicotine is absorbed by the mucous membranes of the mouth.[4] Used properly, the gum produces nicotine levels sufficient to prevent withdrawal symptoms.[5]

Effectiveness. A 1987 meta-analysis[6] reported that nicotine chewing gum, when used in specialized smoking cessation clinics, produced significantly higher cessation rates than placebo gum at 6 months (27% vs 18%) and 12 months (23% vs 13%), but not in general medical practices. A 1995 meta-analysis[7] reported that 2-mg nicotine chewing gum produced better quit rates than placebo in 15 studies involving more than 7,000 smokers recruited from family practices. Despite initial gains, 1-year follow-up abstinence rates averaged a very modest 3% greater than with placebo. Over-the-counter use of nicotine gum produced quit rates of 13% after 6 months (compared with 8% for placebo gum), which led the investigators to conclude that when adjunct psychosocial treatment was not provided, overall quit rates were quite low.[8] However, in the placebo-controlled trials, nicotine gum (and the nicotine patch) still increased quit rates by a factor of 1.6 to 2.8 over placebo.

Evaluation of outcomes was complicated by the fact that some persons continued gum use as long as 2 years after smoking cessation.[9] One large-scale review[5] noted that approximately one third of patients continued to use nicotine gum 6 months or longer after cessation, and that abstinence dropped by 50% as users ceased gum use from 6 months to 1 year after smoking cessation.

Side effects. Common side effects include gastric distress (hiccoughs, nausea and vomiting) and jaw muscle ache; however, tolerance to most side effects usually occurs within the first week.[10]

Nicotine patch

The nicotine patch has been available in the United States by prescription since 1991,[11] and over-the-counter since 1995.[8] Transdermal application makes it easy to use and eliminates the oral side effects reported by nicotine gum users. Applied once daily and left on for 18 to 24 hours, it is most commonly available in 7-, 14-, and 21-mg strengths. Appropriate dosages correlate with the number of cigarettes smoked per day by the former smoker. Gradual weaning is recommended to reduce nicotine withdrawal effects.

Effectiveness. A 1994 meta-analysis[11] found that patches containing active medication were superior to placebo patches regardless of type, treatment duration, weaning, counseling format, or counseling intensity. At the end of treatment 27% of patch users and 13% of placebo users were abstinent; at 6 months, 22% of patch users and 9%, of placebo users were still abstinent. No benefits were gained by extending the treatment more than 8 weeks, however; studies with shorter treatment durations were not included in the analysis.

Some manufacturers recommend that their patch be worn a full 24 hours and others recommend that it be worn only about 16 hours and removed at night. The 16- and 24-hour patches were equally effective by the end of treatment (25% and 27.9% abstinence rates, respectively), and only slight differences were recognized at the end of 6 months (18.7% and 24.7% abstinence, respectively).

Although data at 1-year follow-up were not in the 1994 meta-analysis,[11] other studies that include 1-year follow-up data have reported quit rates ranging from 9.3% to 26.2% for patch users, vs 2.8% to 20.8% for placebo groups. Silagy et al[12] analyzed the results of nine patch studies, six of which included abstinence rates at 1 year. Unfortunately, much of this data was pooled, with abstinence rates calculated according to the "longest follow-up available." Nonetheless, quit rates were calculated at 20.5% for nicotine patch users vs 10.6% for placebo. Other reports at 1-year follow-up ranged from 9%[13] to 25%.[14]

As other investigators have consistently found,[3] Fiore et al[11] demonstrated that nicotine replacement coupled with psychological intervention was more effective than patch use alone. At the end of treatment, patch users

Urge each smoker to quit—physician advice is the most effective motivation

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who had participated in group (vs individual) counseling had higher abstinence rates (41.4 vs 28.8%). More intensive behavioral counseling, (measured by meeting frequency, attendance requirements, number and frequency of meetings) also significantly enhanced cessation rates, almost doubling the likelihood of successful quitting. At the end of treatment, 41.5% of patch users in the "high intensity" category were smoke-free, but only 22.8% of the "low intensity" subjects were smoke-free. At 6 months, however, the results were more modest (26.5% abstinent for high intensity; 19.5% abstinent for low intensity).

As would be suspected, success rates in randomized, controlled trials do not necessarily generalize to over-the-counter usage. A more recent review summarized the results of five over-the-counter nicotine patch studies which indicated that without psychosocial treatment, abstinence rates were quite low, ranging from 9% to 11% at 6 months (vs 4% for placebo). The rates for physician-prescribed patches were similar, ranging from 5% to 12%.[8]

Side effects. Common side effects include skin irritation, insomnia or vivid dreams, and nausea.[10,15] Skin reaction can usually be reduced by rotating the patch site.

Some people keep using nicotine gum for a year or more

Nicotine nasal spray

Nicotine nasal spray delivers nicotine via the nasal passageways and mucosa. Nonsmokers are instructed to use one or two doses per hour for up to 3 months. Peak nicotine levels occur within 10 minutes and are approximately two thirds those of cigarettes. Although the rapid nicotine delivery (quicker than gum or patch, but slower than cigarettes) has been touted as beneficial,[8,16] this is debatable. The rapid psychoactive "hit" from nicotine spray may reinforce nicotine-seeking behavior and keep the nonsmoker from effectively breaking the nicotine-reinforced linkages associated with smoking. Substantial proportions of those using the spray continue to use it for 1 year or more following cessation of smoking.

Effectiveness. Reported success rates at 6 months range from 16% to 35%,[17,18] and in general doubled the quit rates compared with placebo.[8] It should be noted that in one of these studies,[18] 10 of the 34 "successful" nonsmokers continued to use the spray at the 1-year follow-up. Sutherland et al,[19] in a study combining nicotine nasal spray and group treatments, found 26% to 28% abstinence rates at 1 year, while the placebo groups were 10% to 13% successful.[4] At 1-year follow-up, 43% of abstainers continued to use the nasal spray.

Side effects. Common side effects include nasal and throat irritation, rhinitis, sneezing, coughing, and watery eyes.

Nicotine inhaler

With an appearance similar to a cigarette, the nicotine inhaler consists of a hollow, plastic stick and plug that provides nicotine vapor when inhaled. As with the nicotine gum, the inhaler delivers nicotine through the mucous membranes of the mouth. As such, its mechanisms of action are similar to that of the gum.[20] Even though it delivers less nicotine than cigarettes, the behavioral similarities between inhaler use and smoking may make it difficult for some quitters to break the associations between nicotine use and daily activities, thus making it more difficult to remain abstinent.

Effectiveness. A review of four nicotine inhaler studies[8] observed that, at 6 months, three studies reported cessation rates of 17% to 21% in treatment groups and 6% to 9% in placebo groups. One study found no difference between the inhaler and placebo groups. Higher results have been reported (28% successful at 1-year follow-up); however, 16% of the nonsmokers continued to use the inhaler.[21]

Side effects. Common side effects include throat irritation and coughing.

BUPROPION

Although the specific mechanisms by which bupropion (Zyban, Wellbutrin) works as an aid to smoking cessation are not clearly understood, a positive correlation between smoking and mood disturbance has been well documented. Nicotine is known to have stimulant and depressant effects on the central and peripheral nervous system, including specific interactions with brain dopamine, serotonin, endogenous opioid peptides, pituitary hormones, catecholamines, and vasopressin.[22]

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Patients receiving bupropion while undergoing smoking cessation appear to experience fewer nicotine withdrawal side effects than do patients receiving placebo; however, their baseline depression scores are not affected by the treatment.[23]

Effectiveness. In the early 1990s, bupropion was noted to contribute to spontaneous smoking cessation in a group of veterans who were undergoing bupropion treatment for depression. This led the researchers to conduct a randomized, controlled trial involving 190 nondepressed smokers, using a 300-mg/day dose of bupropion, vs a control group. In addition to medication, each participant also received 16 weeks of group behavioral treatment. At the end of 4 weeks, 40% of the bupropion participants were deemed successful abstainers compared with 24% of the placebo participants.[24]

Subsequent multisite, placebo-controlled research[25] has indicated that at the end of 6 weeks, treatment groups that used bupropion at 150 mg and 300 mg per day were significantly more successful than those in 100-mg-per-day and placebo groups. Drug treatment began 1 week before a set quit date, and each group received weekly brief counseling and a follow-up phone call 3 days after the quit date. At the end of 1 year, continuous abstinence was significantly greater for the 300-mg-per-day bupropion group compared with placebo. Approximately 24% of participants receiving 300 mg per day were continuous nonsmokers, while 18%, 13%, and 10% of the participants in the other groups (150 mg, 100 mg, and placebo) were still successful at 1 year. Similar findings were reported by Hurt and colleagues,[26] with 1-year abstinence rates were 23% for the 300-mg-per-day group and 12% for the placebo group.

In a study comparing bupropion, the nicotine patch, a combination of the bupropion plus the nicotine patch, and placebo,[23] the combined group yielded the highest abstinence rates after 1 year (30.3%, 16.4%, 35.5%, and 15.6%, respectively). The treatment period was 9 weeks, with the target quit date at week 2. The bupropion was prescribed in 150-mg morning doses. A placebo was given in the evening for the first 3 days, and an additional 150 mg was given in the evening on days 4 through 63. Brief (15-minute) weekly, standardized counseling sessions were included.

Side effects. Insomnia, headache, dry mouth, dizziness, disturbed concentration, nausea, constipation, abnormal dreams, arthralgia, and back pain are the most commonly reported side effects.

Contraindications are seizure disorder, current or prior bulimia or anorexia nervosa diagnosis, and current MAO (monoamine oxidase inhibitor) use.

OTHER DRUG THERAPY

Antagonist therapy was hypothesized to facilitate cessation by reducing the pleasurable effects of smoking. Contrary to early expectations, the most commonly used antagonists, mecamylamine and naltrexone, were associated with increased smoking as well as high dropout rates due to side effects.[27–29] Nicotine-mimicking medications, including anxiolytics (tranquilizers), clonidine, and antidepressants have also been examined but have demonstrated mixed results. Anxiolytics have been shown to be quite ineffective.[7] Limited benefits were noted with clonidine, but some users also reported undesirable side effects. Antidepressants as a group have demonstrated little or no efficacy, with the exception of bupropion.

Bupropion plus patch and counseling yielded the best quit rate

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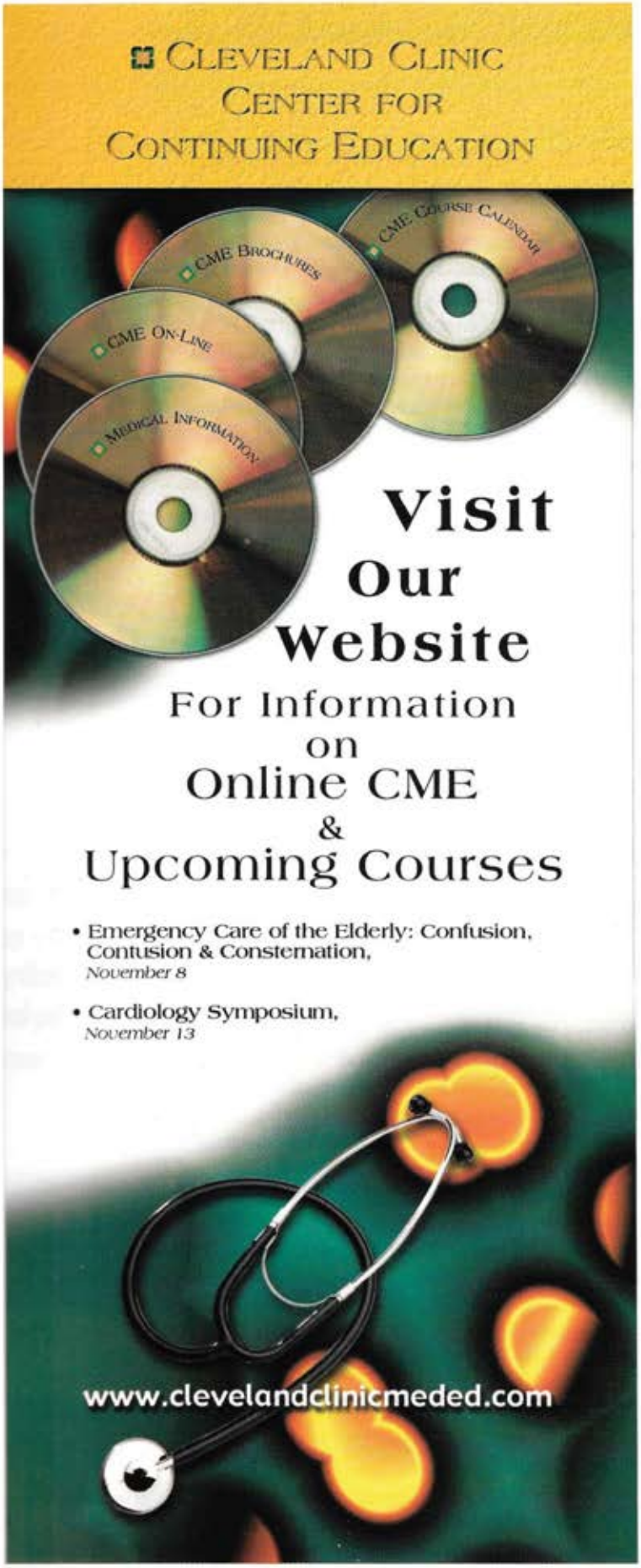

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ADDRESS: *Garland Y. DeNelsky, PhD, Department of Psychiatry and Psychology, P57, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, e-mail denelsg@ccf.org.*

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