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Review Article

An overview of pharmacological aids available to enhance smoking cessation

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SUMMARY Tobacco dependence is a chronic condition that usually requires repeated intervention. Effective interventions exist that can produce long-term cessation at up to double the rate achieved by smokers without treatment. Because pharmacotherapies enhance the quit rates of most other cessation methods, every smoker should be offered appropriate pharmacotherapy to support cessation attempts, unless contra-indicated. A number of pharmacotherapies are effective and safe. Nicotine replacement therapy, antidepressants and other drugs are effective cessation aids.

Introduction

More intervention research is needed to evaluate the effectiveness of other cessation methods such as acupuncture and hypnotherapy.

Tobacco dependence meets the criteria of a drug dependence disorder.[1] In most tobacco users, tolerance develops as well as a characteristic withdrawal syndrome and an inability to control future use.[2] Tobacco dependence warrants medical treatment in the same way as any other dependence disorder or other chronic disease.

Although many smokers succeed in quitting on their own, this is usually after several attempts. Over 90% of unaided quit attempts are not successful.[2,3] Use of appropriate pharmacotherapies could double or triple cessation rates.

Types of pharmacotherapy

A variety of pharmacological interventions for treating tobacco dependence have been evaluated in recent years.[4] These include:

- nicotine replacement therapies such as chewing gum or transdermal patches and the less common aerosol inhalers, nasal sprays and lozenges (these are not all available in every country);
- anxiolytic medications to reduce the anxiety symptoms associated with withdrawal;
- some classes of antidepressants, including bupropion SR (Zyban) are now available for use in Australia as well as the US and UK; and
- a variety of other pharmaceutical therapies such as clonidine, nortriptyline, mecamylamine, naltrexone and silver acetate.

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Guideline recommendations

Nicotine replacement therapy (NRT) is considered a cornerstone of smoking cessation in the US[5] and the UK.[6] The UK guidelines recommend NRT or bupropion for people who smoke 10 cigarettes or more per day.[6] The US and Scottish guidelines recommend that all smokers be offered appropriate pharmacotherapy, with NRT or bupropion as a first choice unless contraindicated.[5] Although there has been concern about the safety of NRT in smokers with cardiac disease, empiric studies have shown the nicotine patch is safe in patients with stable cardiac disease.[5,7]

The US clinical guidelines[5] recommend caution when using NRT within two weeks of a patient experiencing a post-myocardial infarction, or in those with serious arrhythmias and those with worsening angina.

Nicotine replacement therapy

The aim of nicotine replacement therapy (NRT) is to provide some of the nicotine from cigarettes minus the harmful constituents contained in tobacco smoke. NRT reduces withdrawal symptoms associated with smoking cessation and makes it easier to avoid smoking by replacing some of the nicotine obtained from smoking.[8]

Types of NRT

There are several different forms of nicotine replacement therapy:

- chewing gum (2 mg and 4 mg doses);
- transdermal patches (16 hour and 24 hour in varying doses);
- nasal spray;
- inhalers; and
- sublingual tablets and lozenges.

Nicotine chewing gum and transdermal patches are the most frequently used and researched forms of nicotine therapy.

Nicotine chewing gum contains a nicotine resin complex that is absorbed directly through the buccal

mucosa, resulting in plasma concentrations which are approximately half that produced by smoking a cigarette. It is available as either a 2 mg or 4 mg preparation and in many countries is sold without a prescription from a medical practitioner.

Transdermal patches are available in several different sizes, and deliver between 7 mg and 22 mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers.[3]

Nicotine gum, nicotine transdermal patch, nicotine nasal spray, nicotine inhaler and nicotine sublingual tablets/lozenges all increase quit rates at 5–12 months approximately twofold compared with placebo and regardless of the setting.[5,9] One study that directly compared four of the six products found no difference in abstinence rates or withdrawal discomfort, although compliance was lower for inhaler and nasal spray.[10] Highly dependent smokers (20 or more cigarettes per day) benefit more from 4 mg than 2 mg gum.[9]

Wearing a patch only during waking hours (16 h/day) is as effective as wearing it for 24 h/day.[9] Eight weeks of patch therapy was as effective as longer courses and there was no evidence that tapered therapy was better than abrupt withdrawal.[9,11]

Combining different forms of NRT are more effective than one form alone with higher abstinence rates at six and 12 months when a combination of nicotine patches and inhaler is used compared with placebo patches and inhaler (25% *vs.* 22.5% at 6 months, 19.5% *vs.* 14% at 12 months).[12] The combination of bupropion SR with a nicotine patch was found to be more effective than a nicotine patch alone.[13]

Side-effects

There are a number of side-effects which may occur with each therapy (**Table 2**).

Pregnancy: The US,[5] UK[6] and Scottish[14] guidelines cautiously recommend NRT when a pregnant woman is otherwise unable to quit and when the likelihood of quitting, with its potential benefits, outweighs the risk of NRT use or continued smoking.

A small non-random trial of nicotine patch use by pregnant women beyond 24 weeks found no adverse effect on fetal status.[15]

Availability of NRT

Nicotine replacement therapy is available as a transdermal patch (7 mg, 14 mg and 21 mg strength) without prescription from pharmacists. This provides smokers with an opportunity to receive advice from pharmacists at the point of purchase.

Barriers to access should be reviewed and addressed. The UK recently elected to make NRT available through a wider range of retail outlets and settings (i.e. not restricted to pharmacies). Saudi Arabia should consider this also. Proponents of wider distribution outlets for NRT argue that it should be as readily available as cigarettes themselves and more accessible to smokers wanting to quit.

There is no subsidization of the cost of NRT for consumers in Saudi Arabia. A smoker using the patch for 10 weeks (an average course) will incur a comparable cost to purchasing cigarettes over the same period.

If NRT is made available at a reduced cost, the use of NRT will increase where there is evidence to suggest that reducing out-of-pocket costs for NRT increases both use of NRT therapies and cessation outcomes.[16]

Table 2 Possible side-effects of nicotine replacement therapy

Nicotine gum
Mild and transient (majority of users)
• mouth soreness, hiccups, indigestion, jaw ache and unpleasant taste
More severe side-effects (less than 2%)[2]
• irritability, lightheadedness, headache, excessive salivation and anorexia
Nicotine patches
• minor skin irritations at patch site (up to 50% of patch users)[2,6]
• insomnia (up to 25% of users)[7]
R*are side-effects*
• headache, dizziness, fatigue, gastrointestinal distress, sweating, limb pain and palpitations
Nasal spray
Common (most users)
• nose, throat or eye irritation
More serious (up to 25% of users)[2]
• nausea, headache, dizziness and cold hands and feet
Nicotine inhalers
Common side-effects (up to 50% of users)[2]
• throat irritation and coughing
Less common side-effects
nausea, bad taste in the mouth, dizziness, gastrointestinal, disturbances and oral burning sensational

Anti-depressants

Bupropion SR

This is a non-nicotine aid to smoking originally developed and marketed as an antidepressant. It blocks the re-uptake of dopamine and norepinephrine centrally.

Use of bupropion SR approximately doubles cessation rates compared to placebo, 30.5% (95% CI = 23.2, 37.8) versus 17.3%.[17]

When used for smoking cessation bupropion is initiated 1–2 weeks before the target quit date and is generally continued for three months.

Bupropion is contra-indicated in people with seizure disorders, a current or prior diagnosis of anorexia nervosa or bulimia, use of a monoamine oxidase (MAO) inhibitor within the previous 14 days or using other medications that contain bupropion.

Nortriptyline

This is a tricyclic antidepressant that blocks uptake of norepinephrine and serotonin. Use of nortriptyline is estimated to triple smoking abstinence rates at five months or more compared to placebo cessation rate, 30.1% (95% CI = 18.1, 41.6) versus 11.7%.[17] Sedation, dry mouth and lightheadedness are common side-effects affecting at least half of users.[2] Extreme caution is advised if used in patients with cardiovascular disease due to risk of arrhythmias, changes in contractility and blood flow.

Nortriptyline is an efficacious smoking cessation treatment. It may be used under a doctor's supervision as a second line agent to treat tobacco dependence.[17] When used for smoking cessation treatment it is initiated 2–4 weeks before the quit date and continued for approximately 12 weeks.[2]

Fluoxetine

This is a potent and selective inhibitor of neuronal serotonin reuptake. Fluoxetine reduces food intake and increases resting energy expenditure, resulting in moderate body weight loss during use[18] and reduction of weight gain in smoking cessation.[19] Use of fluoxetine significantly increased abstinence rates from 20% in the placebo to 30% in two treatment groups at six months follow-up in a multicentre trial.[20]

Fluoxetine, compared to placebo, increased the likelihood of abstinence at one and three months among smokers with minor depression but not those with little or no depression.[21] Fluoxetine was used in conjunction with cognitive-behavioral therapy.

When used for smoking cessation, treatment is initiated two weeks before the target quit date and is generally continued for at least three months.

Fluoxetine may aid smoking cessation in depressed smokers.[21]

Other pharmacological aids

Clonidine

This is a centrally acting adrenergic agonist that dampens sympathetic nervous system activity. The main rationale for use is to reduce tobacco withdrawal symptoms, especially cravings. It is used primarily as an antihypertensive medication. It may be administered transdermally or orally. Smokers using clonidine are started on the drug several days before quitting and maintained on a fixed daily dose for several weeks.

The usefulness of clonidine is limited by appreciable sedation and postural hypotension.[22] Local skin irritation is common with transdermal clonidine. Adverse effects if ceased abruptly include nervousness, agitation, headache and tremor, accompanied by a rapid rise in blood pressure and elevated catecholamine levels.

Mecamylamine

This is a nicotine antagonist. The rationale for use is its potential to block the rewarding effect of nicotine, therefore reducing smoking. There is no evidence for its effect on smoking cessation if used alone, but in combination with NRT, it may be superior to NRT alone.[23]

Naltrexone

This is a long-acting opioid antagonist. In humans, smoking one or two cigarettes significantly increases plasma endorphin levels, leading to the theory that endogenous endorphins may reinforce smoking behavior.[24] Clinical trials failed to detect a significant difference in quit rates between naltrexone and placebo.[25]

Anxiolytics

Anxiolytics increase the production of dopamine, serotonin and norepinephrine, low levels of which are associated with the urge to smoke. They may also reduce the anxiety that occurs with nicotine withdrawal. However, there is no consistent evidence that anoxiolytics aid smoking cessation.[26]

Silver acetate

Silver acetate produces an unpleasant taste when combined with cigarettes, thus acting as an aversive therapy. It is sold in the form of gum, lozenges and spray. Little evidence exists for a specific effect of silver acetate in promoting smoking cessation.[27]

Other interventions

Acupuncture

This is promoted for a range of health-related issues and problems, including smoking cessation. The most commonly cited rationale for use of acupuncture in smoking cessation is that it relieves the discomfort of nicotine withdrawal.[2] There is no evidence of a specific effect of acupuncture in smoking cessation other than as a placebo effect, as there was no difference in cessation rates between 'active' acupuncture and 'inactive' or sham acupuncture procedures.[28,29]

Hypnotherapy

This is proposed as an aid to smoking cessation by influencing underlying impulses which weaken the desire to smoke, strengthen the will to stop and/or increase concentration and increase ability to focus on a treatment program.[30]

Most of the studies in the scientific literature are either case reports or poor quality uncontrolled trials that show a great variability in quit rates (4–88%) six months after treatment.[31,32] Therefore, there is insufficient evidence to recommend hypnotherapy as a specific treatment for smoking cessation.

Conclusion

Tobacco dependence is a chronic disease that deserves treatment. Effective treatments have now been identified and should be used with every current and former smoker. This review provides primary care physicians with the tools necessary to effectively treat tobacco users. The recent increase in effective pharmacotherapy for smoking cessation provides primary care physicians with a wide range of treatment modalities. When used correctly, all currently approved products appear to be equally efficacious. It is therefore logical that the patient's preference, comorbidities and adverse effects profile of individual agents should guide treatment choice. Physicians should be aware of the special needs of certain populations of smokers, including women, light smokers and patients with cardiovascular diseases. Physicians may consider the efficacy of smoking cessation interventions as low compared with that of treatment with antibiotics

or antihypertensives. However, smoking cessation should be put into proper perspective. If physicians achieve a 5% quit rate in 70% of smokers seen yearly, this will result in thousands of smokers quitting each year. There is no clinical intervention available today that can reduce illness, prevent death and increase quality of life more than tobacco treatment interventions.

Summary of implication for the GP

Nicotine replacement therapy

All forms of currently available NRT should be promoted as effective cessation methods, either alone or combined with a behavioral intervention.

- Wearing a patch only during waking hours (16 h/day) is as effective as wearing it for 24 h/day.
- Nicotine replacement therapy is effective on its own but there are added benefits of combining it with a behavioral intervention.
- The combination of bupropion SR and nicotine patches is more effective than nicotine patches alone.

Anti-depressants

Use of bupropion SR (Zyban) for smoking cessation should be accompanied by behavioral counselling.

Other pharmacological aids

- There is sufficient evidence to recommend clonidine as an effective pharmacotherapy for smoking cessation to be used under medical supervision when appropriate. There are insufficient controlled trials to make recommendations concerning the use of mecamyaline, anxiolytics, naltrexone, silver acetate, acupuncture and hypnotherapy for smoking cessation. However, indications from existing evidence are that they are no more effective than placebo.
- Highly dependent smokers who use nicotine gum should use 4 mg not 2 mg doses.
- Smokers with a history of depression may be more successful at cessation using bupropion SR or nortriptyline.
- Patient preferences and expectations regarding outcome are important in guiding choice of pharmacotherapies.

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