Therapy for Cessation of Smoking

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Abstract

Tobacco dependence is a chronic relapsing medical illness. Unfortunately more than 1.1 billion people worldwide smoke tobacco. Tobacco consumption rate is very high in India. Providing three minutes counseling by physicians doubles the cessation rate as compared to no intervention. Nicotine replacement products (gums, transdermal patch, nasal spray, inhaler and lozenge), bupropion and varenicline used with counseling by physicians double the cessation rates at one year. There are drugs like buspirone, naltrexone, mecamylamine and silver acetate; some of which either alone or in combination with any of the above drugs may be routinely used in near future for smoking cessation in at least some specific groups of population. The most difficult problem for patients in smoking cessation is withdrawal symptoms. Counseling with continuous support from physician, family members, friends and overall from the society will help in achieving a higher rate of smoking cessation, with the final aim of making ours a tobacco smoke-free world for future generations.

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Key Words : Smoking cessation; Nicotine replacement therapy; Bupropion; Varenicline

Introduction

The World Health Organization estimates that worldwide 1.1 billion people smoke, aged 16 years and above. Eight hundred million of them are in the developing countries like India and China. Tobacco will become the single leading cause of death [1]. Cigarette consumption is declining in developed nations, but unfortunately, it is increasing at the rate of 3-4% in the developing nations.

Smoking is probably the most important cause of morbidity and premature mortality in the world. Half of all time smokers will die prematurely as a result of tobacco use [2]. There are three main smoking products used by Indians; in order of use they are bidi, cigarette and chutta [3]. Overall toxicity as measured for nicotine, carbon monoxide, hydrogen cyanide, carcinogenic hydrocarbons, benzopyrene and radioactive uranium is higher in bidi than in cigarette [4]. About 70% of smokers want to stop, yet only 2-3% succeed in doing so permanently each year without help [5]. The benefits of giving up smoking are unquestionable and extend beyond the smokers themselves. Individuals and their families gain from reduced spending on cigarettes and improved quality of life. The health care system benefits from reduction in the expenditure and workload caused by smoking-related diseases. The employers stand to gain in terms of better work attendance and productivity.

Clinical Problems

Nearly all smokers acknowledge that tobacco use is harmful to health but underestimate the magnitude of their own risk. Smokers have a higher rate of success when they seek help for quitting [6]. The main physiological obstacle to quitting is the addictive nature of nicotine. After inhaling smoke from a cigarette, arterial nicotine levels increase markedly within 15 seconds. This bolus of nicotine activates the brain-reward system by increasing dopamine release. Nicotine causes tolerance and physical dependence. When tobacco use is stopped, there is a withdrawal syndrome characterized by irritability, anger, impatience, restlessness, difficulty concentrating, insomnia, increased appetite, anxiety and depressed mood [7].

Symptoms of nicotine withdrawal are nonspecific and vary widely in intensity and duration. Symptoms begin a few hours after last cigarette, peak 2-3 days later and wane over a period of several weeks or months, most commonly within first three months. Weight gain of two to four kilograms after smoking cessation is common. This is a concern for a few smokers who are contemplating quitting. Large weight gains are uncommon [8].

Smokers who are more dependent and difficult to treat have the following characteristics; smoke more than 20 cigarettes a day; smoke within 30 minutes of

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getting up from bed; history of significant withdrawal symptoms and early relapse on previous attempts to stop; current or past history of psychosis and dependence on alcohol or other drugs.

Smoking cessation should be attempted at every level; national, institutional, physician, and smokers themselves.

National level

Initiatives for smoking prevention and cessation at national level should include the following measures; increase public education and information about the health hazards of smoking; regulate marketing of tobacco products; preclude access to tobacco products by adolescents; limit promotion of cigarette smoking; increase tax on tobacco products and increase number of smoker-free places and work places.

Some positive measures taken at the national level include the following:

- Government of India, cigarettes and other tobacco products Act 2003 – prohibits smoking in public places, prohibits selling of tobacco products to minor below 18 years and also prohibits advertisement of these products.
- No tobacco day is being observed since the year 1988 on 31 May. Educational advertisements are carried out in media and workshops are also conducted in various cities.
- A tobacco control cell has been established in Ministry of Health since August 2000 with the aim of coordinating activities related to tobacco control. Ministry of Health has also opened 13 tobacco cessation clinics all over India.

Institutional level

Ban on smoking at work places is already being practiced in various institutes in developed countries, and is being strongly argued for or already being implemented in developing countries like India.

Interventions by Physicians

Randomized, controlled trials conducted in primary care practices demonstrate that a physician's advice to stop smoking increases the rates of smoking cessation among patients. Providing a brief period of counseling (three minutes) is more effective than simply advising the patient to quit. It doubles the cessation rate, as compared with no intervention.

Therapy for Smoking Cessation

Two approaches have strong evidence of efficacy for smoking cessation: counseling and pharmacotherapy [10]. Each is effective by itself, but the two in combination achieve the highest rates of smoking

cessation. The Food and Drug Administration (FDA) has approved the following products for smoking cessation: nicotine replacement products (gum, transdermal patch, nasal spray, and inhaler), bupropion and varenicline.

Nicotine Replacement Therapy (NRT)

This involves substituting one form of nicotine delivery for another (e.g. patches or gums for cigarettes). The rationale is to 'wean' smokers off their nicotine addiction through step-wise reductions in dose size or frequency over time, while decreasing the severity of nicotine withdrawal symptoms [10]. The absolute quit rates depend on the level of accompanying support [11]. The pharmacokinetic properties of available products differ, but none deliver nicotine to the circulation as fast as inhaling cigarette smoke does. The patch provides a relatively stable, fixed dose of nicotine over a period of 16 to 24 hours. The other products have a more rapid onset and a shorter duration of action, allowing the user to adjust the dose of nicotine. Blood nicotine levels peak 5 to 10 minutes after the administration of nicotine nasal spray, 20 minutes after the user begins chewing nicotine gum or uses an inhaler and 2-4 hours after the application of nicotine patch. The nicotine gum and inhaler have similar pharmacokinetic properties since nicotine is absorbed through the oral mucosa in both.

Although nicotine's haemodynamic effect increases the myocardial workload, nicotine-replacement therapy is safe in patients with cardiovascular disease, including stable angina. Unlike smoking, nicotine-replacement therapy does not increase the coagulability of blood or expose a patient to carbon monoxide or oxidizing gases that damage endothelium. Therapy should be continued as long as the patients feel that they need it, provided they are maintaining abstinence. However, therapies for more than six months signal a need for re-evaluation of ongoing issues.

Nicotine Gum

Nicotine polacrilex, better known as nicotine gum, is available as 2 and 4 mg preparations. Heavy smokers (those who smoke more than 20 cigarettes per day) are given 4 mg dose [12]. Ten to fifteen pieces are required initially to achieve abstinence. Patients are instructed to chew nicotine gum slowly until they feel mild tingling, which indicates nicotine release. The patient should then place the gum between the cheek and gums of the teeth for seven minutes before chewing it again. This cycle will allow gradual buccal absorption, and should be continued for about 30 minutes per piece of gum. Duration of treatment is three months. Side effects are sore jaw and dyspepsia.

Nicotine Patch

It is easy to use and delivers high doses of nicotine transdermally. The standard dose of nicotine patch is 22 mg. In heavy smokers, 44 mg patch therapy is found safe. A 16-24 hours patch is required to be applied for eight weeks. Side effects are skin reactions and insomnia. Patch sites should be rotated. 1% hydrocortisone is applied for skin reaction. A 16-hour patch is given to a patient who suffers from insomnia [13,14]. If a patient continues smoking after seven days of starting therapy, the quit date should be terminated with the intention of trying again at a later date.

Nicotine Nasal Spray

It requires patient counseling and education to ensure appropriate use. The medication should be sprayed against the lower nasal mucosa where it is absorbed. One spray (0.5 mg) into each nostril equals one dose (1 mg). Patient is advised to start with one or two doses per hour and is also advised not to exceed five doses per hour or 40 doses per day. Most of the patients require about 15 doses per day, with a gradual decrease in the number of doses over time. Nasal irritation is common with nasal spray therapy; however it usually subsides with time. Therapy is usually discontinued by 12 weeks, but some patients may require longer use (up to 6 months).

Nicotine Inhaler

It consists of cotton impregnated with 10 mg of nicotine and enclosed in a small capsule, which the delivery device punctures on closure. When the user puffs on the device (which resembles a cigarette holder), vaporized nicotine is delivered to the mucosa of the mouth and posterior pharynx, where it is absorbed. About 80 puffs over 20 minutes are needed to obtain 2 mg of nicotine. The initial daily dose is six to sixteen capsules. Hence it should be used with caution in patients with asthma. Duration of therapy is six months with dose tapering in last three months. Cough, rhinitis and local irritation are frequent side effects.

Nicotine Lozenge

It is available in 2 mg and 4 mg preparations. It is used in the following dosage : weeks 1-6: 1 lozenge every 1-2 waking hours, weeks 7-9: 1 lozenge every 2-4 hours, weeks 10-12: 1 lozenge every 4-8 hours. Patients should not eat or drink 15 minutes before using the lozenge, and also should not use more than 20 lozenges per day. Side effects of the preparation include insomnia (less than 5% cases), nausea, headache and cough (transient).

Bupropion

It is the first medication which does not contain

nicotine and is useful for smoking cessation therapy. It is an aminoketone antidepressant. It has both noradrenergic and dopaminergic activity. Norepinephrine and dopamine play important roles in the development of nicotine dependence. Nicotine stimulates the release of these and other neurotransmitters. Release of norepinephrine in the locus ceruleus activates higher cortical functions, such as alertness, concentration and memory. Nicotine also activates neurons in the mesolimbic system, which results in enhanced dopamine release in the nucleus accumbens, which is known to be a pleasure-reinforcing area in the brain of addictive drugs. Bupropion is a weak inhibitor of synaptic reuptake of norepinephrine and dopamine. The drug has also been shown to antagonize nicotinic acetylcholine receptor function [15]. All these actions of the drug may result in attenuation of withdrawal symptoms. Enhanced dopamine activity in brain may maintain stimulation of pleasure-response areas in the absence of nicotine.

One potential benefit of bupropion is that it causes less weight gain as compared to other smoking cessations therapies [15]. Therapy is begun with 150 mg once daily in the morning for 3-4 days. If this is tolerated, 150 mg is added in late afternoon or early evening. Patients may continue smoking for the first week of therapy, until a steady bupropion level has been established. Patients are advised to stop smoking during the second week. Therapy may be continued for 3-4 months (6-12 months in selected patients) [16]. Combination of bupropion and nicotine replacement therapy may be required to be given to smokers who have relapsed or could not achieve abstinence with nicotine replacement medication alone. The drug is well tolerated and side effects are few. Common side effects are insomnia (35-40%), headache and dry mouth (10%). Bupropion lowers the threshold for seizures and is contraindicated in patients who are at risk for seizures. The risk of seizure associated with the use of bupropion is 0.1%. The drug has a favorable cardiovascular tolerability profile [17]. There is no evidence to suggest that the drug is associated with an increased risk of sudden death [18]. The likelihood of successful cessation with bupropion is not reduced in patients previously treated with bupropion [19]. Abstinence rates at the end of one year of using some of the above mentioned modalities are: nicotine patches 10.0-11.1%, nicotine gum 10.8%, nicotine inhaler 10.5-10.9%, and bupropion 18.5-23.0% [20].

Varenicline

It is an $\alpha\beta 2$ nicotine hereditary factor X (Stuart-Prower factor) acetylcholine receptor partial agonist. It works by reducing the smoker's urge to smoke and by relieving craving and withdrawal syndromes. Treatment is started one week prior to the target quit date. The

drug is given orally, 0.5 mg daily for first three days, 0.5 mg twice daily on days four to seven, and then the dose is increased to 1 mg twice daily for 12 weeks. An additional 12 weeks of treatment can be given to reduce the chance of relapse. Varenicline is superior to bupropion in both efficacy for achieving abstinence from smoking and in delaying smoking relapse [21,22]. The drug is well tolerated. The main side effect is nausea which can be reduced by taking it after food and with a glass of water.

Other Drugs

Nortriptyline has been found effective in smoking cessation in two small studies that used 75 to 100 mg of the drug daily for three months, starting 10 to 28 days before the quitting date. No other antidepressant or anxiolytic agent has been found useful in smoking cessation. Treatment with clonidine in doses 0.1-0.4 mg/day for 2-6 weeks reduces the symptoms of nicotine withdrawal and has been found effective for smoking cessation, but the high frequency of adverse effects like dry mouth, sedation and constipation limits its use. Buspirone is a serotonergic agonist and anxiolytic. It has been used in a dose of 15-30 mg/day in divided doses for smoking cessation. It is non-sedative and does not have addictive potential. However it has not been found very useful in smoking cessation.

Naltrexone is a long acting form of opioid antagonist naloxone. It has been found beneficial for smoking cessation in female smokers with major depression. Side effects of the drug include drowsiness, disorientation, nausea and abdominal pain. This drug requires to be evaluated in a large control trial before it is accepted for regular clinical use in smoking cessation.

Mecamylamine is a noncompetitive blocker of nicotine receptors, therefore it does not precipitate withdrawal symptoms. Silver acetate may be used as a gum or pill. It combines with the sulphides in tobacco smoke to produce a bad taste, but the compliance is very poor with this drug. Synthetic tobacco substitutes such as cellulose have been tried as a tobacco substitute, but this was not found to be useful [23].

Nicotine Vaccine

Antibodies against nicotine inhibit its passage to brain, thus preventing its addiction-reinforcing activities. Three nicotine vaccines are under investigation at present. These vaccines offer promise in the management of relapse following cessation of smoking [24].

Combination Therapy

Higher abstinence rates are achieved when a nicotine patch is combined with ad libitum use of either 2 mg gum or nasal spray [24]. At present, the use of

combination NRT is reasonable in moderate or highly dependent smokers who have failed cessation with monotherapy, particularly if withdrawal symptoms were prominent.

Clinical Strategies

Every physician should begin with the five A's - ask, advise, assess, assist, and arrange.

Ask: Physicians should ask patients about tobacco use status at every visit.

Advise: Once tobacco use status has been identified, physicians should advise all tobacco users to quit. Even brief advice to quit by a physician results in greater smoking abstinence rates. The advice needs to be personalized to the patient's individual situation. The doctor should tie tobacco use to current health/illness, economic costs, and the impact of tobacco use on children or others in the household.

Assess: Physicians should make an assessment of nicotine dependence of the patients. Qualitative assessment of dependence can be done by asking the subject whether it is difficult for him to refrain from smoking and whether there is a history of failed attempt to quit tobacco [25]. Table 1 shows the Fagerström test for nicotine dependence. This is a simple test for the degree of quantitative assessment of nicotine dependence [26]. It predicts the ability to stop smoking.

Table 1
Fagerström test for nicotine dependence

Question	Answer	Score
How soon after you wake do you smoke your first cigarette?	Within 5 minutes	3
	5-30 minutes	2
	31-60 minutes	1
	Over 60 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
Which cigarette would you most hate to give up?	The first one in the morning	1
	Any other	0
How many cigarettes per day do you smoke?	10 or less	0
	11-20	1
	21-30	2
	Over 30	3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Score	Rating
0 to 2	Very low dependence
2 to 4	Low dependence
5	Medium dependence
6 to 7	High dependence
8 to 10	Very high dependence

If there is no opportunity to apply the Fagerström test, the number of cigarettes smoked daily and the interval between waking and first cigarette will give a rough guide for nicotine dependence. Some long-term smokers have minimal dependence. They smoke small numbers of cigarettes, and may cease smoking for short or longer periods without withdrawal symptoms. This group should be identified, as they are usually able to quit smoking without pharmacological assistance. After providing a clear, strong and personalized message to quit smoking, the physician should determine whether or not the patient is willing to quit at that time. If the patient is not willing to make a quit attempt at that time, the physician should try to motivate him to quit.

Assist: The doctor should assist the patient to develop a quit plan. In preparation for quitting, the patient should set a quit date, ideally within 1-2 weeks. The patient should tell his or her family, friends, and coworkers about the quit attempt and request understanding and support. It is important for the patient to anticipate challenges to the planned quit attempt, particularly during the critical first few weeks (e.g., withdrawal symptoms like negative mood, urges to smoke, and difficulty concentrating). The patient should remove tobacco products from his or her environment and prior to quitting avoid smoking in places where he or she spends a lot of time (e.g., work, home, car).

All smokers trying to quit should receive pharmacotherapy except; those smoking less than 10 cigarettes/day, pregnant/breast feeding women and adolescent smokers. Choice of a specific therapy amongst five first-line pharmacotherapy for smoking cessation (bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch) approved by the US Food and Drug Administration (FDA) should be guided by factors such as cost, physician familiarity with the medications, contraindications for selected patients, patient preference, previous patient experience with a specific pharmacotherapy (positive or negative), and patient characteristics (eg, history of depression, concerns about weight gain).

Arrange: Arranging follow-up contact is the final step in treating tobacco use and dependence. The physician should schedule a follow-up contact soon after the quit date, preferably within the first week. This early follow-up is recommended because the majority of smokers trying to quit subsequently return to smoking within the first two weeks. Repeated physician advice increases the cessation rates in those trying to quit [27,28]. Motivational support from health care professional and social support from family, friends and community members is also useful in helping smokers to quit [29, 30]. A second follow-up contact is recommended within

the first month after quitting. During the follow-up the physician should congratulate any success the patient has had, identify problems that have already occurred, anticipate new challenges to abstinence and assess pharmacotherapy use.

If the patient has used tobacco, the physician should discuss the circumstances surrounding the lapse and attempt to elicit a re-commitment to quitting. It takes most smokers two or more attempts to successfully quit smoking. Each time the patient relapses, he or she learns more about what will help and what will be harmful for the next quit attempt. Also, relapse is consistent with the chronic nature of tobacco dependence.

Conclusion

Smoking is one of the most difficult practices to shake off. The arsenal of pharmacological agents available for smoking cessation has expanded in the last few years. Physicians should routinely identify patients smoking status, readiness to quit, advise and assist smokers to quit, and offer pharmacotherapy to help them quit. A general approach is to start with a single agent and add a second if the smoker has severe withdrawal symptoms, craving, or difficulty maintaining abstinence. Nicotine-replacement products can safely be combined with one another and with bupropion. The addition of pharmacotherapy to counseling doubles the cessation rate. For physicians and health care systems alike, the challenge is implementing effective treatment in routine medical practice.

Conflicts of Interest

None identified

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Book Review

Fitzpatrick's Dermatology in General Medicine. Klaus Wolff, Lowell A Goldsmith, Stephen I Katz, Barbara A Gilhebre, Amy S Paller, David J Leffell, editors; 7th edition; 2008. Mc Graw Hill Medical. ISBN 978-0-07-146690-5. Pages 2402 (Two volumes). Price INR 8600/-

Medicine, it is said, is an ever-changing science. With cutting edge research and new clinical experience exponentially expanding the realms of medical science, there is a felt need to continually update our knowledge base. 'Fitzpatrick' has remained a highly respected textbook, a 'Bible' in the practice of Dermatology. Even since the first edition of this textbook was released in 1971, newer editions have been introduced earlier than the previous ones; every five years now compared to every eight years earlier; a measure of the accelerating pace of change.

The new edition is different from the previous one right from the moment it is opened. The arrangement and organization of various sections and their contents have been completely reshaped. Basic sciences, which occupied a section of its own in the previous edition, are segregated into its components which are now clubbed along with their sections of relevance, bringing with it the advantage of continuity. Some reshuffling, for instance, moves Kawasaki's Syndrome from the section on 'Bacterial Diseases' to the section on 'Inflammatory and Vascular Disorders'. Section-end references are truncated and readers are directed to a website for the rest, thus re-appropriating premium print space for text.

Along with updating of previous concepts, new chapters on

Public Health in Dermatology, Complementary and Alternative Dermatology, Drug Interactions,

Dermatology in Bioterrorism and Biological Warfare have been added, underscoring globally emerging newer advances in Dermatology which the new age dermatologists should be aware of.

Three column text, new stand-out font, different color codes for headings and sub headings, numerous clinical and histopathological color plates, self explanatory figurative representations, graphs, flow-charts and tables make the assimilation of the vast data a cake walk. 'At A Glance' windows and boxes summarizing the differential diagnoses and treatment protocols give a fish-eye view of various aspects of dermatological disorders, something that is not only crisp and precise but also relevant and easy to remember. The reader gets a ready reference point with flip-book views of section name and representative thumbnail pictures on the free margins of both sides of every page.

In a nutshell, this marvelous textbook replete with latest looks, is a completely revised and updated edition with great clarity and easily 'digestible' reference material. With this edition, 'Fitzpatrick' has further cemented its place in the practice of Dermatology.

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