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Introduction

Tobacco use has had a definite swing in fashion from the early to mid 1900’s. Currently, it is the leading cause of preventable disease in the United States [1]. Deaths attributed to tobacco use account for approximately 20% of the total number of deaths each year in the United States [2]. Importantly, as noted by Bates in the British Medical Journal, most smokers are disenchanted with smoking and would not smoke if they could return to their past [3].

Similar to intravenous opiate use in an addicted person, nicotine is not the primary cause of significant medical consequences or death in the smoker, instead the morbidity and mortality is a side effect of repetitive use of a contaminated drug delivery system [4]. Nicotine is simply the primary addictive agent. People who quit smoking live longer than those who continue to smoke due to a reduction in risk of dying from smoking-related disease. In general, the decline in risk from all causes of smoking-related mortality starts soon after quitting and will continue for the next 10-15 years [5].

What is tobacco and nicotine?

Tobacco is a vegetable that when smoked contains over 4000 chemicals including carbon monoxide, nitric oxide, lead cyanide, 43 known carcinogens and nicotine in the inhaled vapor [6]. Nicotine is a colorless to pale yellow, water-soluble chemical. Tobacco smoke inhalation is the fastest and the most efficient method of nicotine delivery to the brain. In less than 10 seconds after inhalation approximately 25% of the nicotine reaches the brain, a rate that is almost twice as fast as intravenous delivery [7]. Nicotine has a chemical structure that enables it to produce the same type of addictive effects as heroin and cocaine. Nicotine administration, via any route, can produce psychoactive effects, mood alterations, positive reinforcement, physical dependence and tolerance [8].

Actions in the brain

Nicotine exerts its effect in the brain by interacting with receptors in several different regions (Nucleus accumbens, ventral tegmental area, Locus coeruleus). The presence of nicotine causes subsequent activation of the "pleasure center," positive reinforcement, arousal and enhanced cognitive functioning [9,10]. Nicotine exerts an effect on dopamine, serotonin, endogenous opioid peptides, pituitary hormones, catecholamines and vasopressin [11]. A current theory is that nicotine may not be the only psychoactive component in tobacco smoke. It is known that nicotine does not
affect monoamine oxidase (MAO) in the brain. However, utilizing positron emission tomography, it has been shown that monoamine oxidase (MAO) are reduced by 30 - 40% in the brains of smokers. If this hypothesis is true, then a MAO inhibitor, such as Moclobemide, may be of some value in the treatment of smokers [12,13].

Tests to determine tolerance

Like the myriad of tests available to determine dependence to a specific drug or chemical, the test used to determine dependence on nicotine was developed by Dr. K. Fagerstrom and presented in a paper in 1978. The Fagerstrom Tolerance Test, as it became known, is composed of 8 questions, with points for each positive response. The range is 0 - 11 points; 0 points indicate minimum physical dependence and 11 points indicates maximum dependence [14].

Nicotine withdrawal

The signs and symptoms of nicotine withdrawal include: irritability, anger, anxiety, depression, hostility, drowsiness, fatigue, restlessness, decreased alertness, lightheadedness, headache, chest tightness, body aches, hunger, urges to smoke, weight gain, decrease in heart rate, insomnia, constipation and sweats [15]. The popularity and success of nicotine replacement therapy is based on the reduction of these signs and symptoms.

Before starting cessation

As in all addiction treatment, patient readiness and motivation to change is a marker of success or failure. Issues that may be raised and appropriate treatments far exceed this paper’s ability to fairly address this area. However, an extremely helpful approach has been set forth in the "Guidelines for Smoking Cessation," published in 1996 by the Agency for Health Care Policy and Research (AHCPR). The recommendations were meant to be used in a primary care physician’s office, though they can be adapted for use in any setting, with minor modifications. Known as the 5 A’s [16], the components are:

- **Ask**: identify all tobacco users
- **Advise**: urge all smokers to quit
- **Assess**: evaluate the willingness or motivation to quit
- **Assist**: help set a quit date and encourage nicotine replacement therapy
- **Arrange**: schedule follow up

Nicotine cessation therapy

Nicotine dependence can be treated with or without the use of medication, though it is most frequently addressed with a multi-component plan. Behavioral treatments remain the cornerstone of all nicotine cessation treatment programs as nonpharmacologic factors (drug -seeking behaviors, reinforcement by the drug and the environment) contribute heavily to the addictive process and continuation of this behavior [17].
non-medication oriented treatment, the mainstay is self-help groups, behavioral therapies and acupuncture. It has been noted that over the last several years, there is a slowdown in the development of new behavioral approaches as compared to the many pharmacologic advances. Medical regimens have included nicotine replacement products and non-nicotine medications. The rational for using nicotine-replacement agents is that as an agonist, the drug replacement enables the smoker to reduce the amounts of nicotine previously obtained from cigarettes while using a system that has reduced toxicity (there is an elimination of the carcinogens and gases associated with smoking). This new delivery system does not allow as rapid an entry of nicotine into the brain, thus decreasing the almost immediate reward associated with smoking. The reduction in withdrawal allows the patient time to develop coping skills and alternative behaviors so as to remain smoke free [18].

**Behavioral approaches**

Self-help and support groups have been an integral part of all addiction treatment. In a small study by Sperber et al in Israel, they found that a quit rate of 33% in one-year follow up period was possible using this modality, but that importantly, a belief in ones's ability to quit, satisfaction with group meetings and spousal support significantly improved success rates [19]. Self-help materials that are provided as part of health advice or nicotine replacement therapy show no evidence of additional benefit according to the Cochrane Database review [20].

Other behavioral therapeutic approaches include:
- brief interventions
- reduced (gradual taper) smoking
- nicotine fading
- scheduled smoking
- contingency management
- relapse prevention
- cue exposure
- aversion therapy
- hypnosis

**Brief interventions**, usually lasting 5 minutes or less and classically carried out in a medically oriented setting, have demonstrated a 2% success rate as compared to no advice, which has a tobacco cessation success rate of 0.1% [21].

**Reduced smoking** is described as gradual tapering of cigarette consumption before the point of abrupt cessation [22]. Nicotine fading involves the switch to lower nicotine and tar brands [23]. These two modalities have documented only mixed success [24].

**Scheduled smoking** is a method frequently using a timer that progressively increases the inter-cigarette smoking interval [25].
Contingency management, which has had success in the treatment of cocaine addiction, is a contracted reward or punishment system tied into the behavior one is trying to treat [26].

Relapse prevention, with only modest results, notes the role of differing situations and their relationship to relapse, with the development of coping responses [27]. It appears that relapse prevention may be more successful for women than men [28]. A combination of relapse prevention and nicotine replacement has proven to be more successful than either treatment alone [29].

Cue exposure has been tried with little success. This technique uses the theory that cues in the environment are associated with drug use and elicit a conditioned response or drug craving [30].

Aversion therapy has been used in various forms, delivery of an electric shock as the aversive stimulus [31], rapid or satiation smoking where patients are told to take one puff every 6 seconds until mild nicotine toxicity is produced (nausea) [32]. These techniques were not carried out in large controlled trials and offer a potential hazard to the patient with an underlying medical condition [33].

Single session hypnosis for smoking cessation was popularized by Speigel in 1970 and studies have shown 20-25% quit rates at one year [34], though effectiveness is improved by adding other treatments [35]. This practice is considered unproven [36]. No trial has documented markers of tobacco smoke intake to rule in or out successful cessation.

Acupuncture

Acupuncture has recently been studied by He et al and has been found to be effective in the motivated smoker. Anti-smoking acupuncture points were compared to sham points and while both groups reported that the taste of tobacco worsened, 31% of the test group showed complete cessation of tobacco use as compared to 0% in the sham group at the end of the study [37]. However, in direct contrast, a meta-analysis of acupuncture for smoking cessation by White et al reported that the overall quality of the studies they looked at were poor and that acupuncture was not superior to sham acupuncture for smoking cessation. They noted that the studies showed "methodological inadequacies" and were absent of "testable hypotheses" [38].

Nicotine Replacement Therapy

Nicotine replacement was developed in Sweden during the early 1970's as a means to assist in smoking cessation, particularly in submariners [39]. Nicotine replacement therapy is a safe, effective and standard treatment of tobacco dependence [40]. Nicotine replacement therapy products were sold only by prescription until 1996, when nicotine gum and 2 of the 4 brands of nicotine patches became available without prescription [41].
Nicotine gum (nicotine polacrilex, nicorette®)

Nicotine gum, which was approved by the FDA in 1984, is marketed under the trade name Nicorette®. The gum is available in 2mg and 4mg strengths and comes in classic, mint or citrus flavors. The gum is composed of nicotine bound to an ion-exchange resin and then incorporated into a gum base. The dosage refers to the content of nicotine in each piece and not the amount delivered. It has been found that .86 mg of nicotine is absorbed from the 2mg piece and 1.2 mg is absorbed from the 4-mg strength gum [42]. The gum is chewed in a "chew and park" technique and the amount absorbed is affected by the chewing rate and the amount and pH of the saliva, with a lower pH (more acid) inhibiting absorption. The user should start with 2mg and can chew one piece every 1 - 2 hours to a maximum of 30 pieces per day. The 4-mg strength is indicated for the treatment of the highly dependent smoker who smokes more than 25 cigarettes per day or has a Fagerstrom test score of greater than 6 [43]. Benefits of the gum include PRN dosing and limitations include the inability to properly "park and chew" the gum. Nicotine gum has been shown to improve smoking cessation outcomes and a meta-analysis of 39 studies by Silagy [44] reported that the odds of abstinence at 6 months was 1.6 times higher for gum users than controls and that combined with behavioral therapy it afforded the best quit rates. Adverse effects of gum use include jaw pain, mouth soreness, dyspepsia and hiccups [45].

Nicotine patch-transdermal systems (habitrol®, nicoderm cq®, nicotrol®)

The nicotine patch-transdermal system was first approved by the FDA in 1991 and several of the patches were approved for nonprescription use in 1996. The patches differ by construction, the amount of nicotine and the duration of use ranges from 16 - 24 hours. All patches deliver at approximately the same rate of .9 mg of nicotine per hour. Temperature and circulation in the skin affect absorption, with increased temperature or exercise improving nicotine delivery. Many practitioners have thought that the 24-hour patch would be more effective by decreasing morning cravings, though the work of Daughton et al showed no difference in the efficacy of the 16 hour vs. the 24-hour patch [46]. The previous study is in contrast to the study by Shiffman et al that showed superior relief of craving and withdrawal, especially during the first 2 weeks of treatment [47] when using the 24-hour patch. The recommended course of treatment is 8-18 weeks with a slow reduction of the patch dose. However, Tonnessen showed no advantage to using the patch for greater than 8-10 weeks [48]. Advantages of the patch over other forms of replacement appear to be ease of application and steady state dosing, with mild side effects, the predominant of which is dermatologic [49]. The nicotine patch has been shown to be effective in cessation treatment with greater than double the quit rate over placebo and 20 - 30% efficacy at 6 months [50]. The long-term abstinence has been shown to be better than placebo after 2 years (12% patch vs. 3 % placebo) [51]. It has been found that the nicotine transdermal approach is effective when combined with low intensity (brief) nonpharmacologic interventions as compared to nicotine gum, which is not effective with only brief interventions [52]. A controversial approach has been to use higher than normal patch strength for those who are heavier smokers, i.e. 44 mg (2 patches). One study revealed better results [53] and one showed no
difference between the 44-mg and the 22-mg results [54], thus making a case for individualized treatment. The nicotine patch has been well tolerated overall. The complaint of sleep disturbances most likely has been the result of nicotine withdrawal and not as a result of the replacement therapy. Skin reactions, due to the patch, appear to be more prevalent in patients with an underlying dermatologic disorder such as eczema or psoriasis [55].

- **Nicotine inhaler (nicotrol inhaler ®)**
  The nicotine oral inhaler, which became available in 1998, is a cigarette holder-shaped instrument that has replaceable cartridges that each contain 10mg nicotine and 1 mg of menthol.

  Each individual cartridge will deliver up to 400 puffs of nicotine with each puff containing 13 micrograms of nicotine. Eighty (80) puffs are required to obtain the nicotine delivered by one cigarette [56]. The nicotine appears to be deposited in the mouth and the pharynx and not in the lung [57]. In many clinical trials, subjects used the inhaler frequently, with up to 4 -6 inhalers used per day [58] and the efficacy has been reported to be 15% in the first year as compared to 5% in a placebo group [59]. The inhaler does allow flexible dosing as an advantage, though absorption is affected by puff rate, temperature, saliva and pH of the oral cavity, much like that seen in nicotine gum use. The inhaler can be used for 6-12 weeks of successful tobacco cessation, and is then followed by a 25% taper of maximum use every month over the next 3 months [60].

- **Nicotine spray (nicotrol ns ®)**
  The nicotine spray was introduced in Europe in the early 1990's and approved for use by the FDA in 1996. The spray is another form of nicotine delivery that allows for flexible dosing, though at a faster rate of delivery than the gum or the patch [61]. One dose (one inhalation into each nostril) delivered by the release of a mist delivers 1mg of nicotine ( 0.5 mg in each nostril) . The average amount of use is 13 to 20 doses per day, with easier reported use than the gum. As needed (PRN) dosing for the relief of craving is an advantage. The one-year abstinence rates were shown to be 26% in the treatment group vs. 10% in the placebo group, with behavioral therapy being available for all subjects [62].

  The most common adverse effects were nasal irritation, throat irritation, sneezing, watery eyes, running nose, nausea, headache, dizziness, sweats and a cough. Of the 5 adverse symptoms (runny nose, nasal irritation, throat irritation, watering eyes and sneezing) reported by Hurt et al, all but throat irritation decreased significantly during day 1 - 7 of use [63].

- **Nicotine lozenge (commit ®)**
  Lozenges containing nicotine are not a new idea as they were described as early as 1960 by Ejrup. Nicotine lozenges have been recently approved by the FDA in 2mg and 4 mg doses. Early work with lozenges revealed that they were not well tolerated due to strong local reactions on the mucous membrane of the mouth [64].
• **Sublingual tablet**
  The sublingual tablet is not currently commercially available in the United States for routine use. The tablet contains 2mg of nicotine and lasts up to 15-20 minutes when placed under the tongue. There is 50% bioavailability; in highly dependent smokers, two tablets can be used at one time every 1-hour. As with the gum and the inhaler, absorption is effected by the saliva and pH of the mouth. Absorption is decreased if the tablet is swallowed.

**Summary of nicotine replacement therapies**
As noted previously, the nicotine replacement therapies are more effective than placebos, though their effectiveness when measured by abstinence rates decline over time. Gum, patches and nasal spray all show about 40% abstinence at 3 months; at one year all are between 15 - 30%. Different modalities work for different patients, though if there is an issue with noncompliance, the patch may be the best alternative to consider. A useful idea is to use fast-acting methods as a PRN for craving and steady-state methods (patch) to give constant relief from withdrawal [65].

**Other pharmacological approaches**
• **Bupropion (Zyban®)**
  Bupropion was originally marketed as an antidepressant (Wellbutrin®). Bupropion was found to aid in tobacco-cessation therapy and it was approved for use by the FDA as Zyban® in 1997. It is a non-nicotine treatment modality and is sold with a recovery plan (Zyban Advantage Plan®).

  The mechanism of action in the smoker is not known, though it may work through the dopaminergic and adrenergic systems [66]. Negative mood states certainly are a component of nicotine withdrawal [67] and the usefulness of this antidepressant may lie at least partially in this domain. Bupropion has been successful as a cessation modality with 27% abstinence at 6 months compared to 16% in the placebo group as reported by Hurt et al [68]. The dosing recommendations are to start with 150 mg a day for three days, then increase to 150 mg twice a day. A quit date for tobacco products should be set for approximately 1-2 weeks after bupropion treatment starts and the duration of treatment can be up to 12 weeks. Bupropion did not appear to relieve all withdrawal symptoms, though the symptomatology was less with bupropion than with placebo. Weight gain was lessened by the use of the nicotine patch in combination with bupropion as compared to the patch and a placebo pill [69]. Bupropion is well tolerated.

  Adverse effects include dry mouth and occasional insomnia. It should be noted that bupropion is contraindicated in patients with a seizure history, anorexia, bulimia, current use of other antidepressant agents which contain bupropion, and the use in patients on MAO inhibitors within the previous 14 days.
• **SSRI's and other antidepressants and anti anxiety agents**
  Prochazka and colleagues have studied nortriptyline in a randomized double-blind placebo controlled trial. Nortriptyline was started at 25 mg taken at bedtime 10 days prior to the quit day. The dose was then titrated upward to 75 mg per day or to a maximum tolerated dose. They found that there was an increase in short-term cessation (6 months - 14%) and a significant reduction in withdrawal symptomatology [70]. There have been a limited amount of studies, all with small sample numbers utilizing nortriptyline. Precautions should be taken with this medication in patients with cardiovascular disease due to the risk of arrhythmia production.

Several other agents, such as buspirone, fluoxetine and moclobemide have been tried with limited or no success using the premise of attacking the depression or anxiety associated with withdrawal. [71,72,73]. Moclobemide has shown significant success in 6 months versus placebo, but was not significant at 12 months [74]. The anti-anxiety medications propranolol and buspirone have sparse data and their efficacy cannot be accurately determined [75,76].

• **Mecamylamine**
  Mecamylamine is a nicotine antagonist, originally marketed as an antihypertensive medication and discontinued in 1996. Given alone, Mecamylamine may cause an increase in smoking (overcomes the blockade of the nicotinic receptors) [77] or it may block the rewarding effect of nicotine and thus reduce the urge to smoke. A solution to this duel effect was to give mecamylamine with nicotine-replacement patches so that there was an overall reduction in available nicotine receptors and less could be activated. The combination of mecamylamine and the nicotine patch has showed 37.5% 12-month abstinence rates vs. 4.2% with the patch alone [78]. Another benefit of combined use is that the orthostatic decrease in blood pressure caused by mecamylamine was offset by nicotine [79]. The Cochrane review also showed that the combination of the patch and mecamylamine were superior to either agent alone, though the study groups were noted to be small and up to 40 % of the subjects required reductions in dose, usually due to constipation [80].

• **Naltrexone**
  Naltrexone has been tried in smoking cessation due to its use in alcohol dependent patients and the possibility that the endogenous opioids are involved in nicotine use and the reinforcement cycle [81]. Wong et al studied the use of Naltrexone alone and in combination with the nicotine patch and found that there was no significant effect of naltrexone, in success rates or cigarette craving [82].

• **Clonidine**
  Clonidine, an alpha2 noradrenergic agonist, was released as an anti-hypertensive but has found off-label uses in the field of addiction medicine. Clonidine comes in pill and patch forms (Catapres TTS® patches). The transdermal patch has been shown to be more efficacious in some smoking cessation trials [83] though reducing only
some withdrawal symptoms but not increasing smoking cessation success in others [84]. Other studies showed only short-lived effects and most subjects relapsed by 6 months [85]. It appears clonidine may be more effective in women [86] and in smokers with high levels of agitation and anxiety on cessation of tobacco products [87]. Overall, clonidine appeared to approximately double abstinence rates when compared to placebo [88]. Clonidine should not be abruptly stopped and failure to gradually reduce the dose over 2-4 days could result in rebound hypertension, agitation, confusion and/or tremor.

- **Lobeline**
  Lobeline is a partial nicotine agonist that has been used in various formulations as a cessation aid. However, when studies were evaluated by the Cochrane Database, no evidence was available from long term trials showing that lobeline can aid in cessation [89].

**Novel treatments**

- **Vaccines**
  Vaccine use in addiction medicine is in its infancy, with clinical trials presently underway. Apropos to cocaine vaccines, the theory of nicotine vaccines is to either prevent the chemical from entering the brain by utilizing nicotine-protein conjugate vaccines [90] or metabolizing the nicotine in the peripheral circulation. It is hoped that this type of treatment could be used by current smokers attempting to quit and former smokers wanting to avoid relapse [91].

- **Glucose**
  In a small study conducted at St. George Hospital Medical School in England, the hypothesis was that smokers may interpret hunger as craving for a cigarette and abstinence heightens this effect. Chewable dextrose tablets were used and showed significant one month abstinence rates when compared to placebo [92], but there was no difference in weight gain in the study groups.

- **Silver acetate/nitrate**
  This chemical, which has been taken off the market, used aversion therapy as its reported methodology. When combined with saliva, silver sulfide was produced which caused the development of an extremely unpleasant, metallic taste in the mouth. As with other aversion therapies, patient compliance is an issue [93].

**Combination treatment**

Many combinations of various nicotine delivery systems, along with bupropion and other medications, have been tried in order to improve cessation rates, particularly in the higher cigarette-using patient. Kornitzer found that the combination of the nicotine gum and patch gave success results of 34% at 12 weeks and 28% at 24 weeks [65] with virtually no increase in side effects [94]. The patch and nasal spray were combined in a study by Blondal, which showed a 51% abstinence rate vs. 35% using the patch alone at 6 weeks. At 3 months the combination group was at 37% vs. 25% in the patch group.
The nicotine inhaler has also been studied in combination with the patch by Bohadana and the results again show higher cessation rates with combined treatments (19.5% with both vs. 14% with nicotine inhaler and placebo patch at one year) [96].

The nicotine patch has been combined with bupropion and has had good success with 35% abstinence at 12 months when both modalities were used versus 30% for bupropion alone and 16% for the patch alone [97]. A suggested use of these medications is to start bupropion for 1-2 weeks and then add the patch on the predetermined quit date with treatment for 3 - 6 months, during which time the dose of the patch is lowered [45].

Special populations

- Alcohol and other substance users
  Burling reported that tobacco dependence is seen in 85 - 100% of users of alcohol, opioids and cocaine [98] while Kalman reported at slightly more modest estimate of 74-88% [99]. Whatever the exact number is, the health toll of cigarette use on this population of patients is devastating with Hurt and colleagues finding that 50.9% of deaths in a cohort study of addiction treatment patients was due to tobacco related diseases [100]. The relationship of alcohol and nicotine dependence is delineated by Gulliver who demonstrated that in a group of alcohol-dependent patients, the urge to smoke is positively correlated with the urge to drink and exposure to alcohol cues will result in an increased urge to smoke [101]. One of the reasons for not addressing tobacco use in the drug/alcohol using population is the fear, which has largely been shown to be unfounded, that if tobacco dependence is addressed it could lead to other drug relapse. Shoptaw found, in a small study, that there was a positive correlation between smoking abstinence and reduced cocaine use [102]. In a prospective study, Stuyt went one step farther and showed significantly better recovery rates for non- - tobacco users than tobacco users in 12-month recovery rates. This was especially true if the drug of choice was alcohol or narcotics [103].

  The belief that substance-dependent patients would not be willing to consider tobacco cessation is Incorrect, according to Ellingstad's work, which showed that over three - quarters of alcohol abusers who were also smokers, said they would be willing to consider stopping smoking during or after treatment of the alcohol problem [104] when asked. In Frosch's study of methadone-maintained patients, 58% of the patients rated themselves as "somewhat" or "very interested" in a smoking-cessation program [105], making a case for, at least, discussing tobacco cessation with this population. If treatment is considered, it may be important to take into account the work of Marks et al that revealed that alcoholics as a group used nicotine in larger amounts and over a longer time than intended, that they continued their use despite disease morbidity related to tobacco use, had significant tolerance to nicotine and appeared to have a greater degree of withdrawal discomfort [106].

- Mental health disorders
  In general, some basic guidelines for managing nicotine-dependence treatment in the patient with a mental health diagnosis need to be considered. Assessment and
treatment should be carried out by a team knowledgeable in Addiction Medicine and Psychiatry. Relapse can occur during periods of increased psychiatric symptomatology. As with all treatment groups, motivation and abstinence increase success and medications should be chosen with an eye on possible drug-drug interactions [107].

- **Depression**
  It has been shown that nicotine alleviates the negative affect in patients with major depressive disorders [108]. Major depression has been associated with heavy cigarette use and poor smoking-cessation outcomes especially in the dual-diagnosed patient with comorbid alcohol dependence [109]. Mood management must be an integral part of cessation programs in this group of patients. Smokers with a history of major depression were more likely to report depressed mood during cessation than smokers with no history (75% versus 30%) [110]. Bupropion may be the appropriate first-line medication to use in this patient group.

- **Schizophrenia**
  There is an association between nicotine use and schizophrenia, though different from the association seen in depression. High rates of smoking in patients with schizophrenia can be explained by the neuromodulatory effects of nicotine in these patients, as it appears that a defect in sensory gating is improved by nicotine. This defect is expressed as negative symptomatology [111].

According to the work of Dalack et al, schizophrenic patients have significantly higher rates of cigarette use (58% - 88%) as compared to the general population (25%) [111]. George et al in their research found that the use of *atypical* antipsychotic medications (clozapine, risperidone, olanzapine and quetiapine) plus the nicotine patch were superior to *typical* antipsychotic medication (fluphenazine, haloperidol, perphenazine, chlorpromazine and thiothixene) when combined with the nicotine patch. Risperidone and olanzapine were associated with the highest quit rates. At ten weeks 55.6% in the atypical agent group versus 22.2% in the typical agent group were abstinent [112]. Zeidonis and George reported a 10-week smoking-cessation program for schizophrenic patients, which included: nicotine patch or patch and nicotine gum, cognitive therapy, motivation enhancement and education. Of 24 patients, 50% completed the program and 3 stayed abstinent for 6 months. It is noted that there was no change in the course of the schizophrenia [113]. A 7-week smoking-cessation program for schizophrenic patients carried out by Addington et al used the *Freedom from Smoking* program which utilized cognitive and motivational enhancement techniques. Of 65 patients, 50 completed the program and 6 were abstinent for 6 months. Again, there was not change in the course of the schizophrenia, showing that while this population may be resistant, they can be treated for nicotine cessation without adverse effects on the mental disorder.
• **Hypertension/cardiovascular disease patients**
Since nicotine has stimulant effects, there were concerns about the use of nicotine-replacement therapies in the medical patient with heart disease or hypertension. Tanus-Santos and his group showed that the use of the transdermal nicotine system was safe in the mildly hypertensive patient [114]. Nicotine-replacement therapy has been found to be safely utilized in patients with stable cardiovascular disease [115]. McRobbie and Hajek set up the following guidelines for using nicotine replacement therapy in patients with cardiovascular disease [116]:

- recommend its use to patients who have tried and failed to quit without nicotine replacement therapy if there has been a serious cardiac event in the preceding 4 weeks, involve the patient's physician in the decision ensure dosing does not exceed manufacturer's recommendations stop use of the nicotine replacement agents if the patient relapses

- target motivated patients

• **Gender issues**
Women who smoke can not be treated the same as men. According to the work of Perkins, women may smoke less for the nicotine effect and more for non-nicotine effects, such as seeing and smelling smoke, the social pleasures and the rituals involved. Thus, it may be prudent to tailor therapy in women to increase the use of behavioral modalities and not rely as much on nicotine replacement [117].

It has also been noted that women attempting to quit tobacco use are affected by depression, lack of social support and worries about weight gain to a greater degree than men [118]. Women also tend to have a heightened degree of withdrawal symptomatology as compared to men [119] and as previously noted, clonidine may work well in this group, especially if there is a significant degree of anxiety and/or agitation associated with cessation.

Smoking cessation treatment in pregnant women is an important issues. As noted by Klesges, smoking cessation in pregnant patients is one of the most effective ways to reduce adverse outcomes such as fetal growth retardation, preterm delivery and perinatal mortality [120]. However, since nicotine -replacement products are category D, with the exception of nicotine gum which is category C, and Bupropion which is category B (no adverse effects on fetal development have been observed in animal studies, no data from humans available), behavioral treatment options should be tried and encouraged before medications are considered [121]. Medication interventions should be considered if the pregnant women has failed in her attempts without medication [122]. In a small study by Ogburn et al, comparing pregnant smokers and pregnant nicotine-patch users, nicotine levels were similar in smokers and patch users and there was no evidence of fetal compromise [123].
• **Heavy smokers**
As with most medical treatment protocols, there are often patients that require larger doses of medication to attempt a successful outcome. It would be less than scientifically minded to expect the available high dose patch to be sufficient for all smokers. Dale et al presented data that a 44 mg per day dose regimen could in fact be safe and provide better withdrawal symptom relief in the heavy smoking population, again making a statement for individualized therapy [53]. Killen reported different results that did not support the use of higher dose patch therapy. Though he used 15 mg as a standard and 25 mg as high dose [124].

• **Racial groups**
There is a paucity of research pertaining to smoking cessation interventions among minority populations. It has been noted that African - Americans smoke fewer cigarettes, use a higher percentage of mentholated brands and prefer the use of higher tar and nicotine cigarette brands. When compared to white study patients, African - American smokers have an increase in quit attempts and are approximately one-third less successful [45]. However, when four racial/ethnic groups were evaluated (African -American, American Indian/Alaska natives, Asian Americans/Pacific Islanders and Hispanics), African - American men have the highest health risks of these four groups and show a death rate from lung cancer that is 50% higher than in whites. Other tobacco-related cancers are also particularly high among African - American men [125]. Overall, all approved therapies can be used and can be effective in racial and ethnic minorities. It is essential that all materials and explanations are conveyed in the patient's language.

• **Patients who fail**
In patients who fail attempts at tobacco cessation, the healthcare provider must consider harm reduction versus total abstinence. Though certainly not a general recommendation, long-term use of nicotine-replacement agents with a decrease in tobacco byproduct exposure can reduce the medical sequelae associated with smoking. It is suggested by Zellweger that this period of sustained smoking reduction will not impact negatively on future cessation attempts [126]. Hurt et al have put forth another consideration for the severely nicotine dependent patient who has failed treatment, that is they evaluated the utility of an inpatient treatment experience. Twenty-four patients (24) were hospitalized at the Mayo Clinic for 2 weeks.

The patients were treated with a combination of behavioral (group therapy, stress management, exercise), chemical-dependence therapy and transdermal nicotine replacement therapy and showed a 29% continuous abstinence at one year [127].

**Predictor of success**
While no treatment is 100% successful, several factors can predict a higher rate of success according to Tonnesen. He has given evidence that adjunctive behavioral
support and total abstinence from tobacco products in the first week of cessation therapy produce improved outcomes. Another factor is a history of previous quit attempts; patients who never tried to quit show a fourfold lower probability of success than patients who tried previously [128]. Kabat and Wynder in their evaluation of over 5000 hospitalized patients who had a history of tobacco use found that quit rates increased with increasing age, higher education level and a higher occupational level. Whites had a higher quit rate than African-Americans while Jewish patients had higher rates than non-Jews. The more time between awakening and the first cigarette was an indicator of positive quit outcomes. Divorce or separation led to lower quit rates [129]. McWhorter et al, using a cohort of subjects from the First national Health and Nutrition Examination Survey (NHANES I), found that predictors of quitting for one year were older, white, smoked fewer cigarettes per day, had higher household income and hospitalizations in the follow-up period. Predictors of relapse were younger, females who lived in an urban setting [130].

Conclusion
Smoking cessation therapy has continued to evolve and expand over the last few years with new agents and techniques being studied and presented for general use, though there is lack of sufficient data to rank an order of use. However, the mainstay of good treatment is an individualized approach, taking into account all of the patients specific characteristics and needs. The treatment provider needs to take into account his/her familiarity with each medication, efficacy, specific population characteristics, patient preference, prior patient experience with treatments (both negative and positive), the cost of the treatment, ease of use, adverse effects and possible managed care restrictions. What has been evident is that if one does not ask, treatment opportunities are missed and the likely significant health consequences will go unabated.
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