Neural Circuitry

The reward pathway and addiction; Humans, as well as other organisms engage in behaviors that are rewarding; the pleasurable feelings provide positive reinforcement so that the behavior is repeated. There are natural rewards as well as artificial rewards, such as drugs. Natural rewards such as food, water, sex and nurturing allow the organism to feel pleasure when eating, drinking, procreating and being nurtured. Each of these behaviors is required for the survival of the species.
The major structures of the reward pathway include the ventral tegmental area (VTA), the nucleus accumbens and the prefrontal cortex. The VTA is connected to both the nucleus accumbens and the prefrontal cortex via this pathway and it sends information to these structures via its neurons. The neurons of the VTA contain the neurotransmitter dopamine which is released in the nucleus accumbens and in the prefrontal cortex. This pathway is activated by a rewarding stimulus.

Activation of the reward pathway by an electrical stimulus; The discovery of the reward pathway was achieved with the help of animals such as rats. Rats were trained to press a lever for a tiny electrical jolt to certain parts of the brain. When an electrode is placed in the nucleus accumbens, the rat keeps pressing the lever to receive the small electrical stimulus because it feels pleasurable. This rewarding feeling is also called positive reinforcement. The importance of the neurotransmitter dopamine has been determined in these experiments because scientists can measure an increased release of dopamine in the reward pathway after the rat receives the reward. And, if the dopamine release is prevented (either with a

drug or by destroying the pathway), the rat won't press the bar for the electrical jolt.

Addiction; Addiction is a state in which an organism engages in a compulsive behavior, even when faced with negative consequences. This behavior is reinforcing or rewarding . A major feature of addiction is the loss of control in limiting intake of the addictive substance. The most recent research indicates that the reward pathway may be even more important in the craving associated with addiction, compared to the reward itself. The following material is a discussion of the interaction between drugs that are addictive, their cellular targets in the brain, and the reward pathway.

Example: The Action of Cocaine

The action of cocaine; Cocaine is also an addictive drug, and like heroin, not all users become addicted. However, with the advent of crack cocaine (the free base), the rate of addiction to cocaine has increased considerably. The example of cocaine is used because it is very similar to nicotine in terms of route of administration (smoking) and its stimulant effects.

Snorting vs. smoking cocaine: different addictive liabilities; Historically cocaine abuse involved snorting the powdered form (the hydrochloride salt). When cocaine is processed to form the free base, it can be smoked. Heating the hydrochloride salt form of cocaine will destroy it; the free base can be volatilized at high temperature without any destruction of the compound. Smoking

gets the drug to the brain more quickly than does snorting. The faster a drug with addictive liability reaches the brain, the more likely it will be abused. Thus, the time between taking the drug and the positive reinforcing or rewarding effects that are produced can determine the likelihood of abuse. This also holds true for nicotine delivered by various forms of smoked tobacco.

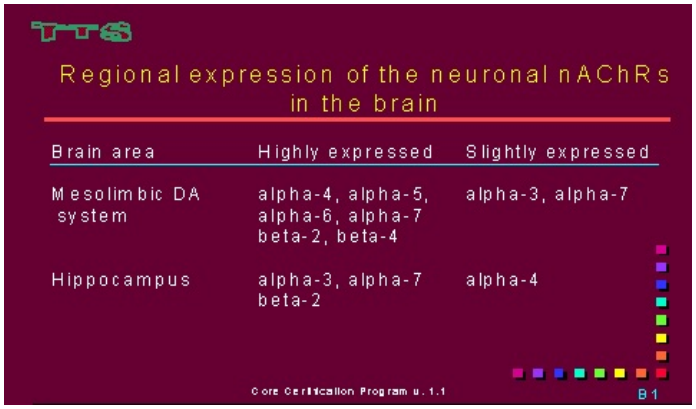
Localization of cocaine "binding sites"; When a person smokes or snorts cocaine, it reaches all areas of the brain, but it binds to sites in some very specific areas, including the VTA, the nucleus accumbens and the caudate nucleus. Cocaine binds especially in the reward areas that you have just discussed. The binding of cocaine in other areas such as the caudate nucleus can explain other effects such as increased stereotypic (or repetitive) behaviors (pacing, nail-biting, scratching, etc.) Cocaine binds to sites in areas of the brain that are rich in dopamine synapses such as the VTA and the nucleus accumbens. Notice the pathway of dopamine transmission in the close-up of a synapse in the nucleus accumbens. Cocaine binds to the uptake pumps and prevents them from transporting dopamine back into the neuron terminal. So more dopamine builds up in the synaptic space and it is free to activate more dopamine receptors. As a result of cocaine's actions in the nucleus accumbens there are increased impulses leaving the nucleus accumbens to activate the reward system. This pathway can be activated even in the absence of cocaine, i.e. during craving. With repeated use of cocaine, the body relies on this drug to maintain rewarding feelings.

Just as heroin (morphine) and cocaine activate the reward pathway in the VTA and nucleus accumbens, other drugs such as nicotine and alcohol activate this pathway as well, although sometimes

indirectly (e.g., the globus pallidus, an area activated by alcohol that connects to the reward pathway).

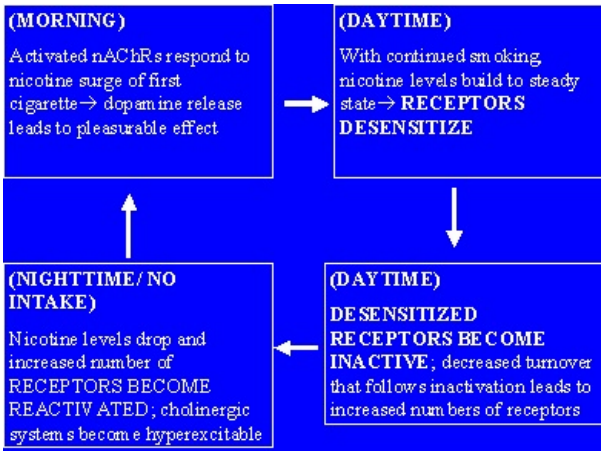
Nicotine's Actions in the Brain

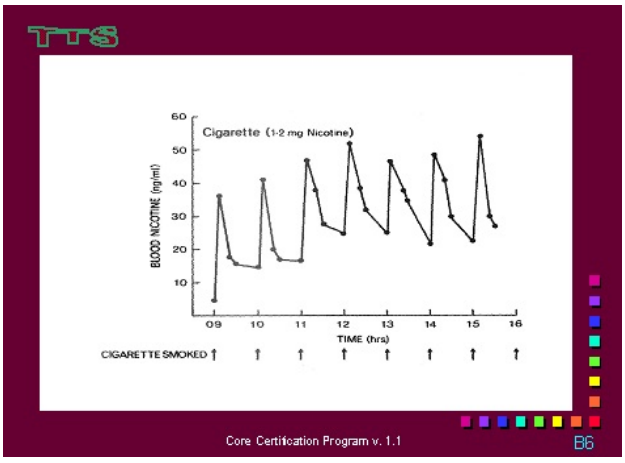
Nicotinic receptors: Subtypes and distribution; Nicotine in tobacco exerts its actions on physiology and behavior by binding to nicotinic receptors in the brain. These nicotinic acetylcholine receptors (nAChRs) are large proteins spanning nerve cell membranes that normally translate the external signal of the neurotransmitter acetylcholine into an electrical signal that affects processes inside the nerve cell. Outside of the brain, nicotinic receptors are found in muscle and nerve cells of the autonomic nervous system, which also contribute to the physiological responses to tobacco. There are two general classes of nAchRs : muscle nAChRs and brain nAChRs, the latter of which concern us here. Despite the many different subunits expressed in the brain, experiments indicate that brain receptors are mostly composed of alpha-4 and beta-2 subunits. One important question is which of the effects of nicotine on the central nervous system are mediated through nAChRs containing the beta-2 unit. It is known that the alpha-7 unit is present at high levels in the hippocampus, an area of the brain involved in learning and memory. It is also known that many nicotinic subunits, including beta-2 and to a lesser degree alpha-7 are present in the mesolimbic dopamine system.



Experiments with gene knockout mice have indicated that the β-2 and α-7 subunits are implicated in nicotine dependence. Scientists have been able to genetically alter mice so that they do not have any β-2 nicotinic brain receptors. These mice show no stimulation of dopamine by nicotine, nor do they learn to self-administer nicotine, compared to mice who have these receptors. This information is important because it might help us to understand individual differences in response to nicotine and therefore nicotine dependence (e.g., those smokers with more or less of the specific nicotinic receptors), and it might help in tailoring new pharmacologic treatments which specifically target these receptors (e.g., by blocking or antagonizing their function, making nicotine less reinforcing).

Dynamics of receptor function; It is also important to understand the dynamics of receptor function in relation to smoking and blood/brain nicotine levels. Neuroreceptors can become more sensitive for various reasons and they can also proliferate, both of which can be referred to as upregulation. Typically, one observes upregulation of receptors as a compensatory response to low levels of a neurotransmitter. Downregulation refers to the opposite, reduced sensitivity or fewer receptors, which in turn serves to compensate for excess levels of a neurotransmitter. In the case of nicotinic receptors, the story is a little more complicated, and can be explained as follows (after Dani & Heinemann, '96): Upon smoking a cigarette, a small pulse of nicotine activates nAChRs that directly or indirectly induce dopamine release that provides a pleasurable effect. With continued use, nicotine builds up to a slow steady-state concentration that causes significant nAChRs desensitization and, over time, inactivation. There is evidence that nicotinic receptor turnover decreases following inactivation, leading to an increased number of nAChRs. In between cigarettes, during sleep, or under conditions of abstinence while attempting to stop smoking, nicotine levels drop and a portion of the inactive nAChRs recover to a responsive state. Because of the increased number of nAChRs that have now become responsive, some cholinergic systems become hyperexcitable to acetylcholine, contributing to the drive for the next cigarette. Thus smokers may medicate themselves with nicotine to regulate the number of functional nAChRs. Note that this is still only a theoretical model, but it explains the powerful reinforcement experienced when smoking after a period

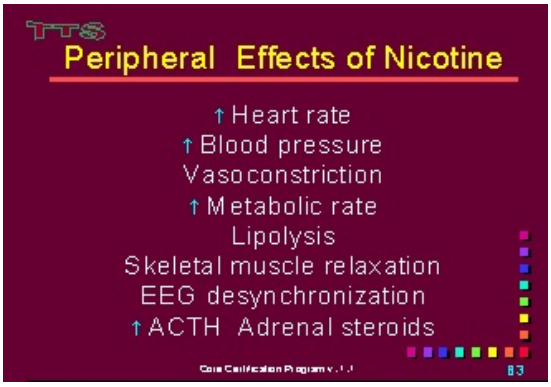




of abstinence, even overnight. Understanding receptor function can also explain the rapid development of tolerance (acute) to nicotine's effects, which would drive continued smoking.

CNS Effects of Nicotine- Implications for Addiction

Neuropharmacologic effects of nicotine; Even though we have focused primarily on the actions of nicotine in terms of its effect on activating nicotinic receptors in the mesolimbic system, which promotes release of dopamine, it is also important to note that nicotine has many effects on different neurotransmitter systems, probably due to the fact that nicotinic receptors of all kinds are distributed throughout the brain. For example, release of norepinephrine can promote stimulation and arousal; acetylcholine has effects in terms of improving short-term memory and cognition (attention); glutamate has similar effects; nicotine also stimulates activity of endogenous opioids, possibly contributing to its stress-reducing and analgesic effects.



Peripheral Effects of Nicotine; Some of the peripheral effects include the following: á Heart rate; á Blood pressure; Vasoconstriction; á Metabolic rate; Lipolysis; Skeletal muscle relaxation; EEG desynchronization; áACTH à Adrenal steroids. Some of these peripheral effects may also reinforce continued use, such as effects on metabolism, and increased circulation of adrenal steroids (e.g., cortisol).

Non-nicotine-related effects of smoking that may be related to dependence: MAO; Recent studies have examined the role of monoamine oxidase A and B (MAO A & B) in the human brain. MAO breaks down neurotransmitters such as dopamine, serotonin, and norepinephrine. Using neuroimaging techniques, it has been shown that cigarette smokers have a reduction in brain MAO B of about 40% relative to nonsmokers and former smokers. Smokers have a 28 % reduction in brain MAO A relative to nonsmokers. MAO A and B inhibition is associated with enhanced activity of dopamine, so inhibition of MAO could be reinforcing. This could also account for higher rates of smoking among individuals with symptoms of depression. Interestingly, nicotine does not inhibit MAO at physiologically significant levels, so some other as yet unknown compounds in tobacco smoke have this property. Currently, clinical trials are underway to evaluate the efficacy of MAO inhibitors for smoking cessation.

Production and modification of nicotine yields; As early as the 1950s, internal tobacco industry documents indicate that the industry considered the cigarette to be a sophisticated nicotine delivery device. Recently, there have been allegations and investigations concerning the spiking of tobacco with additional nicotine. In the process of picking the leaves from the stalk of the tobacco plant, supervisors use a four or five tier system, literally how high the leaves are up on the stalk, to control nicotine yield. Nicotine is more concentrated in the upper leaves, so by mixing the proportion of upper and lower leaves the yield of nicotine can be manipulated very effectively. It is also worth mentioning that nicotine yield as indexed by the "smoke machine" method can be quite deceptive. For example, low tar cigarettes may contain more nicotine than high tar cigarettes. More important, though, is the smokers' tendency to compensate for the manufacturing processes that make cigarettes low yield (e.g., faster burn, less tobacco, ventilation holes) by learning to smoke these cigarettes more effectively, by blocking filter holes, smoking more of the cigarette, puffing more frequently, etc. This is referred to as nicotine regulation.

Summary of smoking-body weight relationship; Women tend to gain more weight than men when they quit smoking (3.8 vs. 2.8 kg). A subset of both men and women (9.8% and 13.4%) are likely to gain a major amount of weight when they quit smoking (i.e., in excess of 13 kg). However, vigorous exercise programs and pharmacologic adjunctive treatments such as nicotine gum or serotonergic agents may hold some promise in preventing post-cessation weight gain.

Implications for addiction; Multiple reinforcing effects of tobacco means that individuals come to depend on nicotine to reliably produce these effects, and may rely increasingly on nicotine to produce these effects as a substitute for obtaining these effects in other ways. This is, in part, a functional definition of dependence: That is, what does smoking do for an individual. It is also important to note that: (1) These effects may be very short-lived (i.e., only a few seconds or minutes in duration; and (2) Tolerance may develop to these effects. What this means is that smokers who have come to depend on nicotine to produce these effects may continually "chase after" these effects as they are less reliably produced in an acute sense. There is also the possibility that

smokers selectively remember the most "reinforcing" smoking experiences in these terms, and this, in turn, drives smoking behavior, to re-experience these peak experiences.

Plasma nicotine concentrations as a function of smoking a cigarette, nasal spray, vapor inhaler, and nicotine gum; Compared to other forms of nicotine administration, cigarettes offer the most efficient delivery and the fastest spike in blood nicotine levels. Using heart rate as a marker, it has been shown that rapid nicotine dosing (i.e., by smoking) produces a much greater effect than does slower administration of a similar dose of nicotine. Likewise, the subjective effects of smoking a cigarette are greater than the subjective effects after nicotine exposure after nicotine gum, which is in turn greater than after transdermal patch delivery of nicotine. It is thought that this rapid exposure to the bolus of nicotine has direct and powerful effects on receptors in the mesolimbic dopaminergic system, and can therefore be particularly reinforcing. Abuse liability of nicotine delivery systems appears to be directly related to the rapidity with which nicotine is delivered. The smoker can manipulate the dose of nicotine on a puff-by-puff basis ("finger tip control"). The intake of nicotine depends on such factors as puff volume, depth of inhalation, rate of puffing, and intensity of puffing. Because of this complexity, the dose of nicotine cannot be predicted by the nicotine content of the tobacco product. Dose can only be determined by blood levels and rate of elimination.

Distribution of nicotine; Smoking is a relatively unique form of systemic drug administration because it enters the circulation via the pulmonary rather than the portal or systemic venous circulation. However, nicotine clears quickly from the brain as it is distributed into other body tissues. This rapid clearance from the brain could have something to do with the need for continuous rapid dosing of nicotine via smoking. Nicotine crosses the placenta easily and is found in the amniotic fluid and umbilical cord blood of newborns. Fetal exposure to nicotine has been associated with developmental problems, predisposition to attention deficit and conduct disorders, and even to later adult criminal behavior.

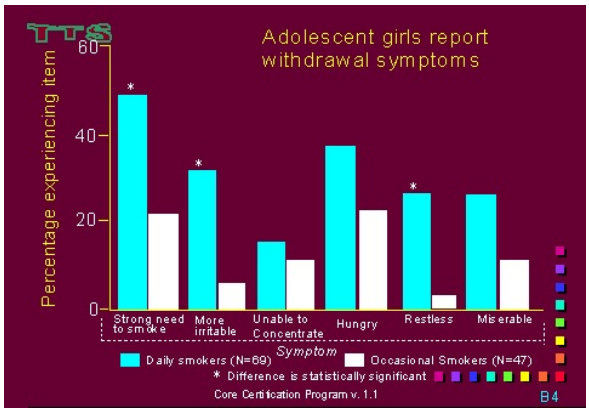
Elimination of nicotine of nicotine; Nicotine is rapidly and mostly metabolized by the liver. Nicotine is eliminated primarily be hepatic metabolism by way of C-oxidation (cytochrome P450) to cotinine, the major metabolite. The half-life of nicotine averages about 2 hours, which is short, but there is considerable variability among people (range, 1-4 hours). The short half life has important

implications for smoking, insofar as smokers need to maintain a steady level of nicotine in the blood, so they will work to constantly dose themselves when they are able to.

Nicotine regulation; Smokers work, consciously or unconsciously, to maintain blood nicotine levels within the "therapeutic window." Evidence for this comes from studies of low tar, low nicotine cigarettes. Research has convincingly demonstrated that smokers will compensate for low nicotine yields by smoking more effectively - blocking filter holes to prevent ventilation of smoke; smoking more of the cigarette; inhaling more rapidly and deeply; smoking more. This, low tar, low nicotine cigarettes are both not safer (from the point of view of carcinogen exposure), and do not show less potential for addiction. In one study, we manipulated the nicotine yield of cigarettes by having smokers smoke through a filter that eliminated 75% of nicotine. Before and after this manipulation, we measured blood nicotine levels. We found that smokers who maintained similar blood nicotine levels after the manipulation (those who worked harder to keep a steady blood nicotine level) were more prone to relapse when they tried to quit compared to smokers who could tolerate a drop in blood nicotine levels (those who did not work to increase their blood levels).

Tolerance definition; Smoking more to achieve the same effects as were achieved previously at lower doses.

Factors influencing development of tolerance; Among the several factors influencing development of tolerance are: exposure to nicotine (both duration of and amount); pattern of exposure (e.g., intermittent exposure vs. steady exposure); learning/environmental factors (pairing of certain stimuli with smoking). The motivational significance of tolerance lies in the possibility that smokers need to smoke more to attain the same desired effects as achieved previously with a lower dose, or that acute desired effects wear of quickly, so that the smoker constantly tries to recapture the immediately prior experience. However, tolerance is not easily assessed (e.g., typically by self-report) and so is probably not very accurate. Moreover, tolerance has never been shown to be related to outcomes among smokers trying to quit.



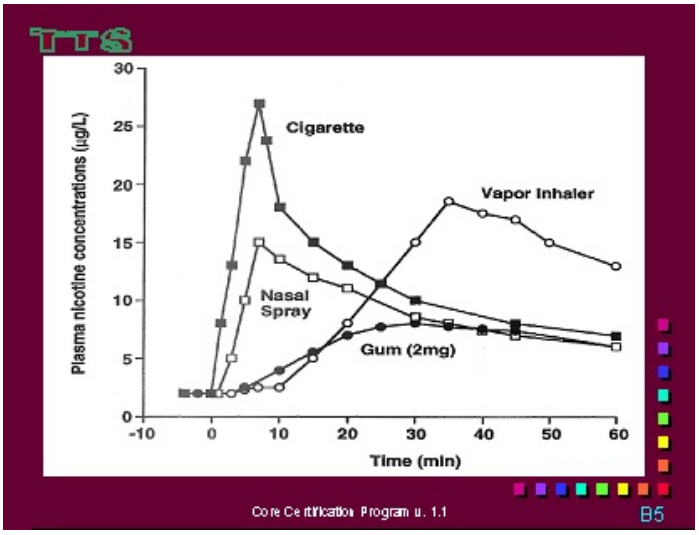
DSM IV Criteria: Nicotine Withdrawal; Along with tolerance, withdrawal is thought to be the hallmark of physical dependence. In fact, some models of drug dependence hold that you cannot have dependence without

tolerance and withdrawal. The time course of symptoms also seems to vary, with most symptoms subsiding within two weeks on average; but craving and appetite increases seem to persist for much longer periods of time.

Treatment of Nicotine Dependence

Types of Nicotine replacement therapy (NRT); There are currently four approved types of NRT, and one that will probably be approved for use soon in the US. Two products, nicotine gum and patch are available over the counter; the remaining products require a prescription. The most popular form of NRT is the nicotine patch. Nicoderm, the patch marketed by SmithKline Beecham, is the one that is available over the counter. Patches differ in their construction and use different mechanisms to regulate nicotine dosage, but all transdermal systems provide relatively similar dosing in terms of pharmacokinetic profiles.

Compared to smoking, nicotine absorbed by the skin patch provides a much slower rise time, but much steadier and stable levels throughout the day. Nicotine provided by the patch replaces about half of that provided by cigarettes, which contributes to its safety, but which might also make it less effective. Therefore, some have advocated increasing the dose of the patch to provide more complete replacement. While this can be done on an individual basis, controlled studies have not demonstrated superiority of doubling the patch dose in terms of cessation outcomes. Among the more common side effects are abnormal or vivid dreams. This is caused by nicotine absorption during sleep. One solution is to use the 16-hour nicotine patch; another is simply to remove the patch before bedtime. The only potential problem with this is that the patient will have to wait awhile the next morning to achieve optimum nicotine replacement, and so could experience some intense urges to smoke. Pharmacokinetics of other forms of replacement show the inhaler and gum to have relatively slow rise times (although faster than the patch). This has to do with absorption of nicotine through the lining of the mouth and tissue in the throat, not the lungs. The gum produces lower blood levels than the patch, and the inhaler is roughly equivalent. The advantage of the



inhaler and gum is that dosing is flexible and controlled by the patient, so higher blood levels could be achieved if needed.

Nicotine gum; The nicotine gums (nicotine polacrilex; Nicorette), were the first form of nicotine replacement. Their efficacy has been demonstrated in both formal treatment and primary care settings, and they are now available OTC. They come in two doses: 2 and 4 mg, with better efficacy demonstrated for the 4 mg dose, probably because of better nicotine replacement. Flavored versions are now available. It has been demonstrated that the gum works best when combined with behavioral treatment. It also works best when chewed on a fixed schedule. There is also evidence that more complete dosing produced by the gum (e.g., 4 mg gum) works better for smokers who are more nicotine dependent as assessed by the Fagerstrom Tolerance Questionnaire.

Efficacy of and estimated abstinence rates for Nicotine Spray; The nicotine nasal spray is a prescription product. It offers the advantage (and liability) of more rapid rise in nicotine levels than any other NRT. Evidence suggests it works best for smokers who are highly nicotine dependent. It also has greater dependence liability. The side effect profile is not great, and includes nasal and throat irritation, rhinitis, coughing, sneezing, and watery eyes. This turns many smokers off of the nasal spray, but some get used to these side effects, so the nasal spray has its place, but will probably never achieve great popularity. It may be a good second line tool for the heavily dependent smoker who has failed with other NRT approaches.

Efficacy of and estimated abstinence rates for Nicotine Inhaler; The nicotine inhaler produces a nicotine vapor when drawn through the tube into the mouth. Nicotine is absorbed by the mouth and throat. Nicotine levels peak in 20 minutes, and approach those achieved by the gum. Side effects are negligible, which is good. The downside of this device is that it takes a lot of puffing to achieve acceptable levels of nicotine replacement. However, because it is shaped somewhat like a cigarette, it might help to deal with some of the oral and handling habit aspects of smoking. In addition, it is unobtrusive.

How does NRT work?; The answer to this question is: We don't know for sure, but we have some pretty good ideas. For the slow acting products (patch, inhaler, gums), it is likely that a lot of the efficacy has to do with blocking or blunting nicotine withdrawal

symptoms, including craving for cigarettes. NRT, however, does not completely block withdrawal, but it may do so just enough to make the process of quitting bearable. Replacement may also make smoking less reinforcing, so that a slip does not progress as easily into a relapse. The faster acting NRT products (inhaler) may approximate some of the reinforcement achieved by the bolus effect of rapid nicotine absorption into the brain by smoking. This is likely to be somewhat true also for the gum, especially the 4 mg gum. Products which require constant dosing may help the smoker cope with the habit aspects of smoking, replacing the oral and handling aspects of smoking. NRT may also allow the former smoker to concentrate on using other behavioral skills that they have learned to keep them from smoking. NRT may also promote fear of negative health consequences (heart attack) if smoking occurs while using NRT.

Bupropion SR – A new approach to smoking cessation; Initial interests spurred by reports of spontaneous quitting in patients being treated for depression. A recent study suggested that Zyban could be used in combination with the nicotine patch, with no increase in side effects. Efficacy of the combination was superior, but only in the short term. In this study, Zyban outperformed the patch alone. Efficacy conclusions: Zyban is effective as an aid to smoking cessation. Zyban exhibits a dose-response relationship for efficacy. 300 mg/day produces the highest quit rates. Zyban is at least, if not more, effective than the patch. Combined use of the patch and Zyban may produce higher quit rates than either treatment alone

Clonidine for nicotine detoxification; Clonidine is an alpha-2 agonist, and inhibits the action of the locus ceruleus. It has been used for detoxification in alcohol opiates addiction. It has been demonstrated to reduce craving in nicotine withdrawal, and to improve smoking cessation. There is some controversy about whether it works better for women than for men, but a recent meta-analysis of studies suggests it is equally effective for both men and women. It is available in pill or patch format. Use in either format should be titrated to avoid hypotension, sedation, and fatigue, which are the primary side-effects because it is an antihypertensive medication. Clonidine should not be considered a first-line treatment for smoking cessation, but it may be useful in suppressing withdrawal symptoms such as irritability, anxiety, and restlessness. Its use with other medications (e.g., NRT) can be considered because of different and possibly complimentary mechanisms of action.

Odds ratios for meta-analyses; In terms of efficacy for smoking cessation, the results of several meta-analyses (a method for combining results across independent studies) show that, compared to placebo, nicotine gum improves quit rates by about 60-70%. The nicotine nasal spray and inhaler are roughly equivalent, improving quit rates at just under two-and-a-half times that compared to placebo. The patch enjoys the best efficacy, with quit rates ranging from double to three times that of placebo. Bupropion comes out pretty well compared to the patch, at 2.6 times the efficacy of placebo. It should be noted that very few studies of bupropion, nasal spray, and inhaler exist relative to the patch and gum, so these numbers may fluctuate as more research trials are conducted.

Smoking cessation products in the pipeline; There are several potentially new compounds in the drug development pipeline. Among these are variations on antidepressant-based treatments, such as a new version of Zyban; testing of MAO A and B inhibitors; testing of existing antidepressants; testing of new NRT products such as the lozenge and sublingual tablet, and esoteric ideas such as a nicotine vaccine.

Behavioral treatments

Nicotine fading: How To's; There may be reasons (medical, personal preference) that a smoker cannot use NRT or other medications. In this case, it is worth considering reducing nicotine intake gradually. First, the smoker must keep a diary of their smoking (amount and brand) over a representative period of time, 3-7 days, depending on variability in the pattern of smoking. Then nicotine intake can be roughly estimated based on the number of cigarettes smoked/day x nicotine content of brand, averaging across days to come up with a daily estimate. Then, the smoker can reduce the number of cigarettes or brand, or a combination of both to reach a target of 25% of the original level over a period of 2-4 weeks. Fading can also be accomplished with commercially available computer-assisted devices such as the Lifesigns product. However, bear in mind that smokers will regulate their nicotine intake upward to compensate for reductions. This type of nicotine fading has three potential effects: (1) It may make withdrawal less intense when the person eventually quits; (2) The person may experience some mild withdrawal during fading, which helps them cope with withdrawal later on; (3) Fading helps a smoker practice going without at least some cigarettes, and so this serves as practice for giving them up entirely. Problems with fading include: (1) Taking too long to reach quit day so that the smoker loses momentum; (2) Fading too quickly so that severe withdrawal is experienced; (3) Fading to more than 25% reduction in nicotine which may not be tolerable.