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Developing a Rational Approach to Tobacco Use Treatment in Pulmonary Practice: A Review of the Biological Basis of Nicotine Addiction

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Abstract

The toll of tobacco use on a pulmonary practice is severe. Physicians, patients, and their families experience frustration, hopelessness and even anger when confronted with a seemingly irrational decision to keep smoking despite morbid lung disease. This paper examines the biological basis of this behavior and seeks to integrate this insight into a rational approach to the problem in practice. Smoking is reexamined within the framework of an irrational compulsion to seek nicotine, despite a rational desire to stop. Control over the compulsion to smoke is established as an important clinical outcome, and the rationale for treating tobacco dependence as a chronic illness is examined. Finally, practical insights into managing ambivalence, including an aggressive pharmacotherapeutic approach based on the neurobiology, are presented.

Keywords

Nicotine Addiction; Nicotine Biology; Smoking Cessation; Tobacco Dependence; Counseling; Behavioral Medicine

Introduction

Treating tobacco dependence can be a frustrating endeavor in clinical practice. Overwhelmingly, physicians report negative expectations about the outcomes of tobacco interventions in the office.¹ Continued smoking despite the enormously motivating nature of respiratory illness is a confusing proposition for patient, family and clinician, frequently undermining the doctor-patient relationship and resulting in missed opportunities for empathy during these especially trying illnesses.² It is well documented that as many as 90% of smokers identify tobacco as harmful and want to reduce or stop using it.^{3,4} On the other hand, the majority of smokers also experience a visceral reluctance to quit, making only very brief and infrequent attempts to stop.⁵

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Cessation attempts are frequently private, even covert, for fear of failure. In an attempt to make it more easily accessible, highly efficacious nicotine replacement therapies (NRT) were approved for over-the-counter purchase in 1996.^{6,7} NRT's practical effectiveness appears to have since declined because of issues such as under-dosing, poor technique, and lack of physician guidance.⁸⁻¹⁰ Deeply held biases frame failure to quit as *de facto* evidence of insufficient motivation. As a result, we attempt to convince. Office cessation can easily feel like a Sisyphean endeavor, with clinicians trying to motivate a burst of will power that may never come.

Suppose instead that the prospect of progressive dyspnea and illness were already in fact as convincing to the patient as they appear *en face* to be. After all, it would take a remarkable level of indifference for patients in a pulmonary practice to ignore the real possibility of morbid disability. Continued smoking could no longer be considered a manifestation of motivation deficit, but instead must be considered a disorder of an abnormally amplified motivation *not* to quit. Consider from your own perspective how substantial the hidden motivation not to quit would have to be in order to outweigh the more overt, rational desire to avoid suffering and shame. A more productive approach to cessation in the office might then involve focusing less intently on the apparent motivations of disease, and instead focusing more on the hidden, abnormally amplified, motivations to continue smoking. Tobacco use treatment becomes reframed, such that it's no longer about addressing the motivations we see, but more about effectively managing the motivations we don't see.

The Nature of Nicotine's Special Effect on the Brain

Hijacking Survival Instincts

In the early 1940s, researchers began developing both animal and human behavioral models for investigating nicotine's effect on the brain. The ability of nicotine injections to re-create the cigarette's distinct psychoactive effects, and the ability of de-nicotinized cigarettes to reproduce the "inner hunger" associated with tobacco deprivation, were both successfully described by 1945.^{11,12} But it wasn't until the 1980s that researchers began systematically demonstrating that nicotine acts as a subtle yet potent psychoactive drug, with motivating effects that could be modulated by the environmental context within which it is administered.^{13,14} Nicotinic acetylcholine receptors are located in all areas of the mammalian brain, but the main effectors of addiction are particularly concentrated in both the mesolimbic dopaminergic (ML-DA) system and the locus ceruleus. These sites are of critical importance to basic survival functions of the organism. The ML-DA system plays a central role in orchestrating survival behaviors by activating an instinctual "appetitive" state, motivating goal-directed behaviors aimed at resolving this instinctive drive, and by influencing the cognitive processes necessary for overcoming barriers to gratification of the instinctive need.¹⁵

A key component of the circuitry of the mesolimbic system is a collection of nerve cells that originate in the ventral tegmental area (VTA), located close to the midline on the floor of the midbrain. Neurons of the VTA send projections to target regions in the front of the brain, including the prefrontal cortex, the amygdala and the hippocampus. Perhaps the most well-studied set of projections are those to the nucleus accumbens, a structure implicated as the brain's main locus of reward, and central to the development of addiction. The VTA is populated by dopaminergic neurons that respond to salient stimuli, including, for example, food, sex, and social interaction. Localized electrical brain stimulation studies suggest that the VTA responds to positive rewarding states as well as to aversive stimuli and stress.¹⁶⁻¹⁹ In this way, the VTA appears to promote a state of generalized behavioral arousal under both positive and negative emotional conditions. Ikemoto and Panksepp conceptualized this idea as the "seeking of safety"; the organism is drawn instinctively toward things that are

adaptive, like eating or sex, and motivated to avoid threatening stimuli, like signals of aggression.²⁰ Though seemingly contradictory, safety and threat are but two sides of the same coin, with generalized arousal an adaptive survival response in both circumstances. The VTA receives “safety/threat” input from the brain’s interface with the outside world, including the sensory cortical areas. The VTA’s inputs are predominantly cholinergic and, importantly, primarily nicotinic (nAChR).^{21,22} Because of this, nicotine has the ability to act as an exogenous ligand that reliably activates endogenous cholinergic receptors in the survival centers of the brain, creating a powerful but artificial safety signal.

Because of its ability to hijack these fundamental survival functions, nicotine is one of the most potent neuropharmacologic drugs of abuse, more capable of compelling behavior than “classical” drugs of abuse, including cocaine, amphetamine and morphine.²³ For example, classical drug self-administration can be effectively diminished by substituting saline infusions to reduce the reinforcing effects of drug.²⁴ Alternatively, the application of mild electric foot-shocks to punish drug-seeking behavior is also an effective extinction technique.²⁵ In contrast, the striking thing about nicotine is that, while it is a weaker primary reinforcer with far fewer hedonic effects than the classical drugs, it is paradoxically a more powerful and persistent motivator of continued behavior.²⁶ Animals switched from nicotine to saline, or threatened with electric foot-shocks, display a prolonged reluctance to give up lever pressing and take a much longer time to achieve extinction compared to other drugs. Another experimental paradigm used to demonstrate the motivational effects of a drug is the progressive-ratio schedule for lever pressing. In this model, the number of presses on the active lever needed to receive an injection is increased progressively with successive injections during each session. Animals subjected to this reinforcement paradigm experience an increasing “response cost” as the interval between reinforcing hits lengthens, and will spend much of their time working to get their drug. In a dramatic display of the persistence of nicotine’s behavior motivating effect, squirrel monkeys conditioned to lever press for nicotine continued to do so even when up to 600 lever-presses were needed for each injection of nicotine.²⁷ The dopaminergic pathway from the VTA to the nucleus accumbens is critical to the persistence of this effect; animals with induced lesions in the mesolimbic system no longer show interest in their substances of abuse.^{28,29}

Clinical Corollary - Hijacking Survival Instincts

A 56-year-old woman who has been smoking for 40 years decides to quit following a visit to her primary care physician for evaluation of productive morning cough. Upon awakening on the morning after the visit, she resolves to never smoke again. After her coffee, she is bothered by a subtle draw to smoke. She attempts to distract herself with work, telephone conversations, reading, exercising, and even eating, but the irrational draw to smoke persists despite her best efforts. After 4 days, the compulsion to smoke continues unabated. She reports a depressed mood and a strong sense of deprivation, hopelessness, agitation, even anger. She states she’s “just not right” and articulates a certainty that a cigarette would make her feel better. She returns to smoking despite her considerable disappointment and frustration.

Creating compulsion: The ineluctable connections between environment and behavior

How then does dopamine produce this persistent and significant motivation in light of the severe negative consequences of smoking? The traditional view of dopamine’s effect was that it acted as a hedonic signal, creating a sense of pleasure or mild euphoria. However, nicotine is highly addictive despite the observation that it produces little, if any, euphoric effects. In fact, the concept of “like” can be effectively separated from the concept of “want”. For example, rats depleted of dopamine will continue to display distinct liking

reactions to sucrose, including rhythmic lateral tongue protrusions, but can no longer motivate the behaviors necessary to obtain sucrose in the face of obstacles.^{30,31} In the human parallel, patients with the dopaminergic defect of Parkinson's disease have normal subjective pleasure ratings for sweet food rewards.³² Instead of euphoria, it appears that dopamine transmission to the nucleus accumbens creates "incentive salience", whereby reward-related cues are imbued with an obsessional quality, transforming them into signals that command the animal's attention. Cues that unexpectedly become associated with the delivery of reward (i.e. a positive prediction error) attain a greater relevance through an increased rate of dopaminergic firing in the nucleus accumbens. Conversely, cues that would otherwise predict the delivery of reward result in pauses in the neuronal signal when the reward is not delivered (i.e. a negative prediction error), and trigger a state of "wanting" for the reward. These phasic bursts and pauses in the nucleus accumbens encode a prediction error signal that shapes behavior to maximize the probability of reward by generating both the motivation to seek, and the gratification of finding.³³

Clinical Corollary – Creating Compulsion

A 65-year-old man who has been smoking 1 1/2 packs per day for 50 years is counseled to quit smoking by his physician. During the office discussion, the physician recommends nicotine polacrilex gum to help reduce craving. On a return visit 1 month later, the patient reports that he has been able to reduce his daily consumption to 5 cigarettes, but that there remain several triggers which result in an undeniable need to smoke. He lists them, including his morning coffee, his meals, and his evening TV ritual. He says he "can't imagine" how he will ever be able to go without these cigarettes, and you note that he even appears dysphoric and ill-at-ease during the discussion. He struggles to find a way to articulate his reasons for not abstaining completely. At the conclusion of the visit, he focuses on the relative benefit he has already enjoyed by virtue of the reduction, and he resolves to keep trying though he has no specific plan on how to proceed.

The Connection to Emotion

Nicotine not only abnormally amplifies otherwise normal connections between sensory inputs and motivation, but has a similar effect on the hard-wired connections between sensory inputs and their related emotions. For example, the sound of a growling dog reliably evokes an appropriate sense of apprehension, while the smell of freshly baked cookies evokes a sense of comfort and safety. In 1949, Donald Hebb described a theory of cell assembly that proposed an anatomic underpinning to these long-term associations. Hebb's postulate is frequently summarized as "cells that fire together, wire together", meaning that a biochemical feedback mechanism exists within the circuit that solidifies the functional relationships between the cells.^{34,35} A number of gene transcription products, collectively referred to as *dynorphins*, have been identified as involved in this feedback.³⁶ Like dynorphins, nicotine has the ability to modify depolarization patterns and influence transcription by acting as an exogenous trophic factor, augmenting some connections while diminishing others. The hallmark of nicotine addiction is the formation of abnormally weighted circuit connections between the instinctive, motivational midbrain structures and the centers related to the generation of emotion in the thalamic, striatal and prefrontal cortical areas of the brain.³³ In effect, nicotine can promote long-term learned associations that take on significant and deadly dimensions: nicotine creates a motivation for the target behavior that is rendered undeniable by the abnormally amplified negative emotional consequences of unresolved compulsion. These associations become hard-wired and persistent over time.

We often refer to smoking as a bad habit. However, this discounts the true nature of the problem. While habits are automatic routines, repeated regularly and without thinking, addictive compulsions are ineluctable, characterized by subjective distress when routine behaviors are forbidden or forgone.

Clinical Corollary – The Connection to Emotion

A 32-year-old mother of two decides to quit smoking when she finds out she's pregnant with her third child. Though she has every intention of quitting, and is highly motivated by her pregnancy, she struggles even with the idea of quitting. The urgency of her situation increases several weeks later when her physician counsels her on the potential ill effects of continued smoking. She relates that she is confused and disappointed, often experiencing a sense of panic when she considers quitting – panic that she may be forced to give up smoking, but also panic that she may not succeed. In a moment of great sincerity, she admits to you that “I desperately want to **want** to quit smoking, but I don't want to quit smoking.” On several occasions in her attempt at abstinence, she has resolved to forego a particular cigarette, only to be faced with a mounting sense of agitation and dysphoria, and the realization that the only way to resolve her disquiet is to simply smoke. “I will definitely quit, but after this cigarette.”

The cigarette as a highly engineered nicotine delivery device

Nicotine's effects are potentiated by the rapidity with which it reaches the brain.³⁷ Following a deep inhalation of smoke, there can be as much as a ten-fold arterial-venous concentration difference that develops within only a few seconds.³⁸ Consequently, the brain can essentially discern individual puffs of a cigarette. The rapid surge in arterial nicotine concentration delivered to the VTA creates the “impact” of smoking, responsible for both the rewarding gratification effect as well as the significant addictive potential of the drug. The cigarette is a particularly well designed nicotine delivery device, capable of producing very rapid peaks in levels carried in arterial blood to the brain.^{39,40} Because it is delivered to the lungs, nicotine absorbed into the pulmonary venous circulation carries high concentrations of nicotine back to the left ventricle, well before substantial mixing and redistribution to the rest of the circulation occurs. In addition, processing techniques unique to cigarette tobacco increase the absorption characteristics of the nicotine contained in the smoke. Nicotine exists in both the protonated and free base forms within tobacco. During processing, cured tobacco is first denicotinized, then later renicotinized in specified concentrations, in order to ensure product homogeneity and improve the flexibility necessary to meet evolving consumer demands. The addition of several compounds, including ammonia, to the tobacco leaf during both phases of production increases the fraction of the nicotine that is in the free base form.^{41,42} Because only the free base form can volatilize from the smoke particulate phase into the gas phase of an inhaled aerosol, and because gaseous nicotine is rapidly deposited and absorbed through the respiratory tract, the magnitude and rate of nicotine delivery depend heavily on the proportion of nicotine elaborated in the free base form when the tobacco is heated.^{43,44}

The physical chemistry of nicotine delivery is highly engineered, constant between product lots, and brand specific.⁴³ This likely contributes to the high rates of brand loyalty observed among smokers since significant variations in delivery characteristics would be expected to result in prediction errors within the mesolimbic system.⁴⁵ Therapeutic delivery devices such as the patch or gum have much slower kinetic characteristics, and as a consequence, neither reproduce the somatic experience of smoking a cigarette, nor carry the same addictive liability as the cigarette.⁴⁶ Though not addictive in themselves *per se*, a small proportion of users may report a prolonged dependence on replacement products. This

generally reflects the patient's prolonged vulnerability to, and need for protection from, relapse rather than a primary *want* for the product itself. Far from prolonging addiction, the slow delivery of nicotine derived from replacement products allows time away from the dramatic spikes produced by the cigarette, speeding recovery and increasing the chances of long term control over the smoking behavior.

Clinical Corollary – The Impact of the Delivery Device

A 62-year-old male COPD patient presents to your office for his routine follow-up evaluation. During your physical exam, you notice a tobacco odor about him, as well as a cigarette pack in the left breast pocket of his shirt. He is affable and attentive when you bring up the subject of smoking cessation, and relates that he has tried to quit on a number of occasions since being diagnosed with COPD three years ago. When discussing various options for nicotine replacement therapy, he replies "That didn't work" or "No, that didn't do anything". When discussing nicotine gum, he relates that he is frightened by the prospect of using it – a friend "became addicted to the gum" and he is concerned about substituting one addiction for another. "Besides," he asks, "won't it just take longer for the nicotine to get out of my system?" He agrees to try the nicotine inhaler, however on his return to your office one month later, states "These really aren't the same as cigarettes."

Addiction as a chronic disease

An aspect of tobacco use treatment that generates significant frustration for all involved is the specter of relapse. While we may understand addiction to be an illness characterized by remission and relapse, it is always painful to watch a patient in desperate need of liberation succumb to the long reach of compulsion, sometimes after months or years of abstinence. At the heart of this cruel encumbrance is a molecule known as CREB (cAMP response element-binding protein). CREB is a transcription factor that regulates the expression of several genes that control the behavior of dopaminergic neurons in the mesolimbic system. When nicotine is administered, dopamine concentrations in the nucleus accumbens rise, inducing phosphorylation of cyclic AMP (cAMP), which in turn activates CREB. Chronic nicotine exposure causes sustained activation of CREB, which enhances expression of its target genes, including those that control the production of dynorphins. In this way, neuronal relationships within the circuit are solidified and strengthened.

Another transcription factor, Δ FosB, appears to exert long term control over gene expression. Because the protein is extraordinarily stable, Δ FosB can remain active for months following nicotine exposure.^{47,48} As CREB helps create connections, Δ FosB is felt to confer persistence to these connections so that associative learning is maintained. The strength of connections may gradually diminish in response to prolonged abstinence, but the connections themselves may never be fully divorced. Nicotine exposure promotes cellular changes including increased receptor density and sensitivity, and increased neuronal arborization, that may never be fully reversed, and that place the affected brain at elevated risk of responding to reward associated cues for many years after the last cigarette. Because of this "priming" of the neuronal reward circuit, we see former smokers who suddenly relapse in response to an unanticipated intense motivation to smoke, and who return to their previous smoking patterns within a short while, even after many years of abstinence. In this respect, physicians should consider smoking the behavioral manifestation of a chronic disturbance in brain biology, a chronic illness at risk for relapse and over which control must be actively maintained long term.

Clinical Corollary – Addiction as a Chronic Illness

A 55-year-old female patient presents to your office for a consultation regarding tobacco use treatment. She previously smoked for over 30 years, but quit 5 years ago after developing mild exertional dyspnea. She has remained smoke free during that entire time, without significant cravings or struggle. Several months ago, she received word that her nephew's military unit would be deployed to an active war zone, prompting long nights conversing with her sister about this stressful development. One night, on a whim, she decided to try a puff of her sister's cigarette, to see what it felt like. It was just as she remembered, and even though she initially remained committed to remaining smoke free, she quickly returned to her previous one pack per day routine. She asks your advice, wondering if she is destined to smoke forever. She is confused and distressed, stating "I don't know why I went back. I'm just stupid I guess. I can't possibly be addicted - I stayed off of cigarettes for 5 years without a problem. I don't know why I don't just stop again."

Guidelines published by the US Department of Health and Human Services, and tool kits produced by pulmonary professional societies, are available online to help clinicians with concise, evidence-based recommendations relevant to this problem.^{49,50} Rather than positioning abstinence as success and relapse as failure, these materials approach tobacco use treatment as a longitudinal process warranting ongoing clinician attention to the level of control over the compulsion to smoke.

A tactical approach to managing tobacco dependence in the clinic

Understanding the compulsion to smoke as the predictable manifestation of nicotine's effects on the brain offers important insight into the management strategy for this difficult problem. The patient's internal conflict between the rational desire to stop smoking and the instinctive desire to avoid the threat of abstinence often manifests in the clinic as intractable, often tragic, ambivalence. Tactics for dealing effectively with ambivalence must form the foundation of tobacco use treatment. Ambivalence is characterized by *approach-avoidance* behaviors, in which patients move closer to the target only to find the fear of consequences simultaneously pushing them farther away. Both approach and avoidance motivations are fundamental to normal human behavior, but become paralyzing when they can't be resolved through typical mechanisms. The physician's role in dealing with tobacco dependence becomes about *beneficent persuasion* - employing tactics designed to systematically undermine avoidance motivators, while encouraging the patient's intrinsic approach motivators.⁵¹

Create Cognitive Awareness

The cornerstone of helping patients overcome ambivalence is the process of turning what is otherwise an intensely visceral phenomenon into a tangible story that can be discussed and deconstructed.⁵² For example, the reluctant respiratory bronchiolitis patient might be engaged in a conversation about her reasons for being reluctant to quit. By gently probing, using non-judgmental and open-ended questions, the physician may elicit one or two important objections, and by giving voice to these concerns can reframe these issues into the core problems to be solved. Rather than focusing on the smoking behavior as the problem, focusing on the abnormal motivations for the behavior can provide tangible intermediate steps to work on that are short of cessation, and therefore much less threatening. Further, allowing the patient to express her concerns provides the backdrop against which to explain the patient's prior experiences. A short conversation about the biological basis of motivation helps to minimize the exaggerated sense of self-blame and responsibility that smokers often

feel, validates the patient's position, and provides a viable framework for working through inevitable obstacles during the quit process.

Correct Affective Prediction Error

Smokers routinely overestimate how difficult life will be without smoking. Evaluating the impact of change necessitates future thinking, and the smoker frequently focuses attention on how things will be different after the change. This disproportionately magnifies the relative impact of perceived differences on the desirability of change, even though the vast majority of factors that influence the smoker's condition will remain unchanged.^{51,53,54} "Sameness" is severely discounted. This effect can be minimized by discussing what the anticipated effects of change will be, guiding the conversation in a manner that encourages the patient to also identify the myriad ways in which things will *not* change. This is not a phenomenon unique to addiction; many aspects of human behavior are driven by this bias. In fact, physicians can gain insight into this effect by examining their own intuitions regarding tobacco use treatment. While tobacco use treatment may feel like it is vastly different than routine daily practice, closer inspection reveals there to be innumerable examples where these tactics are already employed by physicians in their daily patient interactions.

Take Baby Steps

When facing the seemingly overwhelming objective of complete and permanent abstinence, it is not uncommon for smokers to respond with a sense of resignation and hopelessness. Using newfound cognitive insights to redefine success into smaller and more manageable portions allows us to minimize this effect. In addition to making the ambivalent patient more comfortable, this approach has the added advantage of also providing the physician with more realistic measures of success. For instance, success for a given interaction might be defined by the willingness of a reluctant patient to discuss the nature of their ambivalence. Or, in a different circumstance, success might be defined by the patient's willingness to start a medication to assess tolerability. Encouraging this approach while minimizing avoidance may at times require a decision to accept intermediate goals on the way to ultimately achieving abstinence. The tactic of dividing large and overwhelming goals into a series of more manageable and feasible goals should not be confused with either negotiation toward an alternate outcome, or acceptance of infinitesimally small incremental change. Both of these common responses may themselves be recognized as avoidance behavior.

Anticipate Escape

As the motivation to quit smoking becomes more intense, we can expect avoidance behaviors to become equally desperate. An extreme form of avoidance is *escape*. In the clinic, escape behaviors are often manifested as concern over complications. Consider, for example, the patient who reports a series of past elaborate or adverse reactions to whichever cessation medication is offered. This circumstance is particularly frustrating when the treatment obstacles proffered appear trivial compared to the consequences of continued smoking. Physicians may be tempted to interpret escape behaviors as deceitful fabrications. However, remember that the smoker may experience visceral apprehension in response to abstinence threats, and that this dysphoria can be perceived and integrated into the patient's life in a number of idiosyncratic ways. Dealing effectively with escape requires both avoiding the temptation to convince the patient of your own perspective, and developing a systematic way of undermining the escape rationale. For instance, anticipating that a patient offered a nicotine patch may express a preference for self reliance, the physician may choose to frame the application of the patch as an expression of reclaimed autonomy. Similarly, a patient who stops taking varenicline because of concern over psychiatric side effects might

be reassured that your commitment includes vigilant monitoring for unanticipated symptoms, as well as dose adjustments should they occur.

Several misconceptions regarding the nature of treatment exist, and can feed ambivalence. By systematically addressing each of these concerns, the available avenues for escape are diminished. As the stakes are raised, the final common pathway for escape might be *sabotage*. For example, sabotage behaviors may be manifest when the patient begins to set unrealistic preconditions for treatment (e.g. “I can’t afford to gain a single pound”), reassigns responsibility for continued smoking to others (e.g. “My daughter is really acting up right now and I’m totally stressed”), or becomes immutable in their position (e.g. “I really like smoking”). When sabotage is identified, it is useful for the clinician to identify and explain it in a non-judgmental manner, and to ask the patient to describe their perspective more fully (i.e. create cognitive awareness of sabotage).

Offer Questions Instead of Answers

In the face of an identified obstacle to cessation, it is tempting to offer several suggestions for moving forward. On occasion, these well-meant suggestions are repeatedly resisted by the patient, each easily negated in turn with simple but irrefutable statements such as “That won’t work for me” or “I don’t believe in that.” This intractable resistance is a form of sabotage that can quickly frustrate efforts at intervention. The technique most commonly employed to deal with this level of escape is referred to as Motivational Interviewing (MI), and represents a directive method for enhancing motivation to change through reflective listening without confrontation.⁵⁵ MI relies on the notion that people are more likely to be committed to that which they hear themselves defend. Therefore the interviewer seeks to elicit the patients’ own reasons for change, their reasons not to change, and perhaps most importantly, their own solutions to perceived obstacles. For instance, a diabetic patient who finds it impossible to remember to put on his patch in the morning might be asked what technique he uses to remember his insulin. In this manner, the clinician allows unspoken implications to exert their influence by allowing the patient to resolve inconsistencies on his own terms. MI is not a process by which we directly motivate patients to change (e.g. “If you don’t stop, you will die.”) and does not assume deficiencies in knowledge, insight, skills, or motivation. It is a stylistic approach to meaningful conversation with our patients, recognizing that pushing against resistance only amplifies it. Motivational interviewing should not be confused with either an absence of resolve to create change, nor with an overly accommodating or indulgent attitude toward smoking. The conversation remains directive and goal oriented; however, the methods of achieving change rely on interrogatives rather than declaratives.

Tend to Matters of Style

Successful management of nicotine dependence is built upon a foundation of trust. Trust is implicit in the social contract between a physician and patient, but can be easily undermined within the context of this problem. Because the nature of nicotine addiction is often poorly understood by the public, smokers frequently encounter judgmental and accusatory attitudes among their friends and family, often feeling personally culpable for the medical consequences of their addiction. The clinic visit has the potential to unintentionally magnify these feelings if attention is not paid to purposefully creating a safe, non-judgmental environment. There are four “magic words” of cessation practice (Table 1).⁵⁶ Rather than directive instructions on what the physician needs to do or say, they represent goals for interpersonal interaction with the ambivalent smoker.

Aggressively Control the Compulsion to Smoke

Typically, behavioral and pharmacologic management are thought of as distinct, though complimentary, mechanisms of effecting cessation. Instead, pharmacologic support should be thought of as one of the most effective mechanism for minimizing emotional barriers to cessation available to physicians. By reducing withdrawal symptoms, improving control over the compulsion to smoke, and offering a mechanism for the smoker to be actively engaged in addiction treatment, pharmacotherapy represents an extremely powerful tool in dealing with ambivalence.

Generally speaking, as the intensity of tobacco use treatment increases, outcomes improve. Despite common bias to the contrary, tobacco dependence treatment is both cost- and clinically-effective, relative to interventions for other chronic illnesses such as hypertension and hypercholesterolemia. (Table 2)

Several studies have shown that combining two types of pharmacotherapy, one that provides passive dosing producing relatively steady levels of drug in the body (i.e. a controller), and another that allows for easy *ad libitum* dosing in response to acute cravings (i.e. a reliever), is more effective in promoting prolonged abstinence than either alone. Effective, “just-in-time” interventions should be offered to all patients, especially to those who have struggled with a single modality in the past.

When used properly, nicotine replacement therapy (NRT) is an effective method of delivering nicotine safely, and preventing withdrawal symptoms such as irritability, difficulty concentrating, anxiety, restlessness and increased appetite.^{14,57,58} Though the exact mechanism of action of nicotine replacement products remains unclear, they are generally felt to work by decreasing the intensity of negative prediction error signals (i.e. neuronal signals created when the reward is not delivered), thereby minimizing the triggered state of “wanting” for the reward. Because of NRT’s overall reliability, this class represents the foundation of tobacco use treatment. Every smoker, regardless of number of cigarettes consumed or duration of use, should at the least be offered some form of NRT.⁵⁹ The transdermal nicotine patch has the slowest onset of action, but provides the longest and most constant rate of delivery. Because blood levels of nicotine peak 2–4 hours after applying the patch, compared to approximately 5 to 10 minutes after using the nasal spray and 20 minutes after using the gum or inhaler, they are best positioned as a controller medication, used in combination with one or more relievers based on patient preference.⁶⁰ For example, when used in conjunction with the nicotine patch, a piece of 2mg gum may be used every 1 to 2 hours as needed to address breakthrough cravings. For patients unable to use the gum properly, or who cannot tolerate its taste, the nicotine lozenge can also be used to relieve withdrawal symptoms in a fashion similar to that of the gum.⁶¹

Fear of overdose is common, and causes both clinicians and patients to underestimate how much NRT is most appropriate. Unfortunately, many patients forego NRT because of predictable fears regarding addictive potential and safety. This misconception frequently manifests as an escape behavior. Rather than simply attempting to convince the patient to use the patch, a discussion of several important facts about NRT may serve to resolve ambivalence. For instance, compared to the immediate nicotine peaks produced by cigarettes, NRT generally provides a much slower release and absorption of nicotine into the blood, making it a non-addictive and safe alternative to smoking. Overdose is a concern among patients who are unsure of their ability to remain abstinent from cigarettes. Fortunately, patients using NRT who continue to smoke reproduce their baseline nicotine levels, but not higher.⁶² Concerns over myocardial infarction or acute cardiac events undermines confidence in NRT in the very subset of patients for whom continued smoking

represents the greatest risk. However, NRT should be considered safe, even in populations at risk for coronary artery disease.⁵⁹

Bupropion SR is a non-tricyclic antidepressant that acts in part by inhibiting uptake of dopamine from the accumbal synapse.⁶³ Bupropion SR is approximately equivalent in efficacy to NRT monotherapy, but most effectively promotes abstinence and controls withdrawal symptoms when combined with NRT and counseling.^{64,65} Patients should begin bupropion SR at least 7 to 10 days before the anticipated quit date, however it is not uncommon for patients to require longer pre-treatment in order to see the full effect.^{66,67} Varenicline, an agonist-antagonist of the $\alpha 4\beta 2$ nicotinic cholinergic receptors in the VTA, seems to work by partially stimulating the VTA while limiting the effectiveness of nicotine as a ligand. Similar to bupropion, varenicline appears to require initial therapy in excess of the recommended one week pre-treatment period before exerting its maximum effect.⁶⁸ Despite popular concerns, the rate of neuropsychiatric side-effects for varenicline appears to be quite low, and should be considered safe and efficacious.⁶⁹ Typical treatment duration is 3 months, however a 6-month treatment course appears to produce abstinence rates that are superior to those expected with 3 months of treatment.⁷⁰

A rational approach to medication recommendations can be based on an assessment of the severity of illness; in this case, severity defined by the intensity of compulsion to smoke. Pulmonary physicians are familiar with this model in the context of asthma and COPD, in which subjective, objective, and medication use indicators are used to estimate the degree of control over underlying inflammation. Similarly, severity of compulsion can be measured using similar measures, and a correspondingly intense pharmacologic intervention devised. For instance, a patient who consumes 40 cigarettes per day, uses his first cigarette immediately upon awakening, and who has experience severe withdrawal symptoms in the past might reasonably be expected to benefit more from a combination of multiple controllers and aggressive reliever use than from a single patch alone. Additionally, patients who continue to feel vulnerable to the seduction of cigarettes might be encouraged to continue using their medications rather than taper by predetermined schedule. Several excellent tools are available to assist the clinician make rational medication decisions based on level of control over compulsion.⁵⁰

Conclusion

Nicotine dependence has been defined as a chronically relapsing disorder, in which the addict experiences an uncontrollable compulsion to smoke, while the number of environmental cues that can trigger drug seeking behavior expands. Reluctance to quit smoking is not a function of lack of determination or of a deficit in motivation, but instead attributable to the action of nicotine on “survival instinct” centers of the brain. An irrational reluctance to quit, despite very real and potentially destructive consequences, is the *sine qua non* of addiction. Continued use is motivated by a compulsion to smoke, and forgoing smoking results in an abnormally amplified emotional response when this compulsion remains unresolved.

Chronic exposure causes permanent neural changes at many levels. These complex changes result not only in amplification of maladaptive connections within the mesolimbic system, but also in persistence of these connections for long periods following discontinuation of nicotine. For this reason, nicotine addiction must be approached as a chronic condition that requires vigilant control over the compulsion to smoke in order to prevent relapse. Relapse is a characteristic of addiction, and not a sign of loosening resolve. The physician’s role is of course to affect abstinence, but also to ease the dysphoria and agitation that can accompany unresolved compulsion. Smokers should not be asked to choose between protecting their

health and preserving their well-being. Instead, we should strive to help our patients have it both ways.

The cigarette is particularly well suited to induce addiction because of its ability to deliver a high proportion of free base nicotine. Very high peak concentrations of nicotine in arterial blood delivered to the VTA are responsible for creating both impact and addiction. A successful strategy for dealing with this seemingly intractable problem requires a tactical approach to dealing with ambivalence, including aggressive pharmacotherapy. The impact of nicotine pharmacokinetics on the development of addiction provides a rationale for combining sustained release “controller” medications with more acute delivery “reliever” medications to increase the effectiveness of cessation pharmacotherapy while giving the smoker an active means of controlling the appetitive desire generated by mesolimbic activation.

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Summary

Understanding the biology of addiction can help the practicing pulmonologist be more effective in treating the onerous problem of tobacco use. This paper presents insights into this biology, informing a logical approach to aggressive intervention. Tobacco dependence is established as a chronic illness requiring long-term management, and available treatment tactics are reviewed.

Table 1

Four “Magic Words” of Cessation Counseling

• Empathy – <i>Develop a sense of shared experience, including emotional and physical feelings. Remember or imagine being in a similar situation. Attend to the initial attachment; work to project warmth, genuineness, and humanity.</i> • Joining – <i>Develop shared therapeutic goals and objectives; enter into a partnership with the patient within which you each express a commitment to work together to reach shared targets. Work with the patient to overcome extrinsic barriers to cessation, for example direct financially disadvantaged patients to available free resources, or arrange for office staff to pursue prior authorization for cessation medications. Try “externalizing” the need to smoke; i.e. help the smoker recognize the “Logical Brain” as separate from the “Addicted Brain,” – develop the notion of the addicted brain as a common foe to be controlled.</i> • Validation – <i>Confirm that their experience with smoking has legitimate biological cause. Offer evidence that others like them have had similar experiences. Avoid over emphasizing “how difficult quitting can be” since this may unintentionally undermine self-efficacy.</i> • Hope – <i>After years of unfulfilling, albeit typically brief, attempts at cessation, smokers often develop a sense of learned helplessness. Hopelessness is a common impediment to behavior change in addiction. Work to reinvigorate hope by maintaining a positive attitude, emphasizing creative solutions to common problems. Avoid overly energetic, eager or “cheerleading” interactions.</i>

Table 2

Effectiveness and abstinence rates for various medications and medication combinations compared to placebo at 6-months post quit (n = 83 studies). Adapted from: Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. 2008.

Medication	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Placebo	80	1.0	13.8
Monotherapies			
Varenicline (2 mg/day)	5	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Nicotine Nasal Spray	4	2.3 (1.7–3.0)	26.7 (21.5–32.7)
High-Dose Nicotine Patch (> 25 mg) (These included both standard or long-term duration)	4	2.3 (1.7–3.0)	26.5 (21.3–32.5)
Long-Term Nicotine Gum (> 14 weeks)	6	2.2 (1.5–3.2)	26.1 (19.7–33.6)
Varenicline (1 mg/day)	3	2.1 (1.5–3.0)	25.4 (19.6–32.2)
Nicotine Inhaler	6	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Clonidine	3	2.1 (1.2–3.7)	25.0 (15.7–37.3)
Bupropion SR	26	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine Patch (6–14 weeks)	32	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Long-Term Nicotine Patch (> 14 weeks)	10	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nortriptyline	5	1.8 (1.3–2.6)	22.5 (16.8–29.4)
Nicotine Gum (6–14 weeks)	15	1.5 (1.2–1.7)	19.0 (16.5–21.9)
Combination therapie			
Patch (long-term; > 14 weeks) + <i>ad lib</i> NRT (gum or spray)	3	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Patch + Bupropion SR	3	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Patch + Nortriptyline	2	2.3 (1.3–4.2)	27.3 (17.2–40.4)
Patch + Inhaler	2	2.2 (1.3– 3.6)	25.8 (17.4–36.5)
Patch + Second generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2–3.4)	24.3 (16.1–35.0)